by stabilizing microtubules and preventing mitosis. Paclitaxel has a narrow toxic-therapeutic window, and can induce vascular inflammation or necrosis if this threshold is approached or exceeded [7]. Both paclitaxel and rapamycin can interfere with complete vascular healing. Neither of these agents have specificity for vascular smooth muscle cells, and consequently both may inhibit endothelial cell proliferation, an important modulator of vascular healing [8,9].

Despite its name, pimecrolimus is not functionally a rapamycin analogue. It is best classified as a macrolactam ascomycin derivative (tacrolimus analogue) that exerts multiple anti-inflammatory effects including inhibition of IL-2 synthesis via calcinuerin inhibition, inhibition of IL-4, interferon γ, and release of inflammatory cytokines from mast cells. It does not bind to the mammalian target of rapamycin (mTOR) and therefore does not work in directly effecting cell cycle regulation but may do so indirectly via IL-2 inhibition [10–14].

The Conor DES is differentiated by virtue of its reservoirs [15]. A drug that is dissolved in a bioerodible polymer is placed within these reservoirs and released with both directional and kinetic control. There is no surface coating with either drug or polymer. Both preclinical and clinical results using a paclitaxel-based Conor stent have been promising. Efficacy at both 30 and 10 μg has been demonstrated in the longer release (30 day in vitro) formulations but faster release formulations were less effective [7,16]. The reservoir stent design also permits the simultaneous delivery of more than one agent simply by placing different polymer-drug combinations in alternate, adjacent reservoirs. This provides the opportunity to test drug eluting stents with combination therapy. It is possible that by combining two agents with differing modes of action, improved safety and/or efficacy may be achieved as is the case with dual agent cancer chemotherapy. We hypothesize that there is a synergistic decrease of neointimal formation by directly blocking the process of neointimal formation at two critical pathway points, inflammation and mitosis. We further hypothesize that this can be achieved without the expense of vascular toxicity or impaired vessel healing.

The goals of our study were three-fold; First, to determine if pimecrolimus, a predominant anti-inflammatory agent, prevents neointimal hyperplasia in the porcine model; Second, to determine if a combination of pimecrolimus plus a direct anti-mitotic, paclitaxel, act synergistically to inhibit intimal proliferation in this model; Third, to study the effect of these agents on vascular healing, endothelial cell regeneration, and inflammation.

MATERIALS AND METHODS

Stent Preparation

3.0 mm × 16 mm cobalt–chromium coronary stents were used for all parts of the study. These were provided by Conor Medsystems. Each stent has 590 individual reservoirs (each 100 μm in diameter) embedded in the stent. The first group of stents was loaded with ~325 μg of pimecrolimus dissolved in a polylactide-*co*-glycolide (PLGA) erodible polymer. A 325 μg dose was chosen as this was the maximum dose that could be loaded onto the stent due to stent reservoir volume constraints. Different comonomer ratios of PLGA (50:50 and 85:15) were used to vary the release kinetics of pimecrolimus as has been previously described for paclitaxel [7,15,16]. The PLGA 50:50 dissolves 5–6× as fast as the PLGA 85:15. The slow release stent uses only the PLGA 85:15 polymer whereas the fast release stent uses only the PLGA 50:50 polymer. Both stents lack a polymer cap, so that both formulations provide an initial burst release. The faster release kinetic stent was designed for ~50% release in the first 48 hr, with the majority of the drug released over ~10 weeks. The 'slow release' kinetic stent was designed to have a lower initial burst with ~25% of the drug released in the first 48 hr and the remainder to be released over approximately a 6-month period. Release kinetics were initially tested with in vitro studies. Following this in vivo studies were done with explanted stents removed and analyzed to ascertain remaining drug left on the stent. Release kinetics were comparable between the in vitro and in vivo groups, which matched the designed kinesis. A second group of stents were loaded with a combination of pimecrolimus and paclitaxel (Fig. 1). Because of manufacturing constraints only previously programmed formulations could be applied to the stent. Since every other well alternated the drugs, the stents were made such that half of the 325 μg pimecrolimus dose was used per stent, and half of the 30 μg paclitaxel dose (previously shown to be efficacious in the PISCES study) was used per stent. Therefore, the total stent dose of pimecrolimus was 162 μg, and the total dose of paclitaxel used was 15 μg. In terms of kinetics, for pimecrolimus the fast release formulation was used (as this had shown better efficacy than the slow release group in our initial analysis). For paclitaxel, the same polymer formulation was used as in the 30-day release group in the PISCES study, as the 30-day release groups showed the best efficacy in follow-up analyses of the PISCES study [16].

Porcine Studies

In the first phase of the study, 10 juvenile farm swine, 25–35 kg in weight, 3–6 months in age were

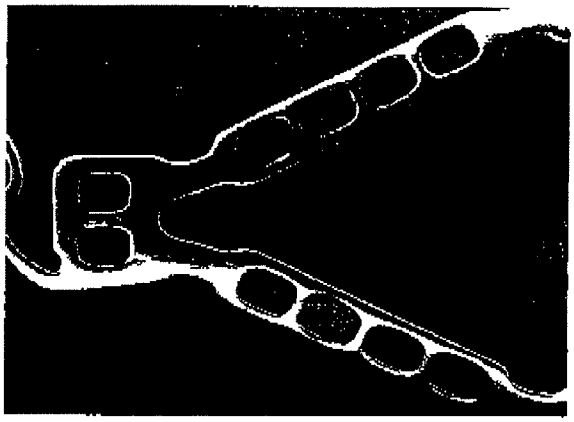

Fig. 1. Close up view of reservoir stents with alternating wells filled with paclitaxel and pimecrolimus. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

enrolled. The two pimecrolimus formulations and a control group consisting of bare metal cobalt stents were evaluated at a follow-up interval of 1 month. In the second phase of the study, seven juvenile farm swine, 25–35 kg in weight, 3–6 months in age were enrolled. One bare metal group and one combination stent group were evaluated at a follow up interval of 1 month. The stents were evenly and randomly distributed throughout each of the three major branches of the coronary arteries (RCA, LAD, and LCX). The artery segment was selected based on vessel diameter and ability to accommodate the length of the stent without excessive curvature. Vessels with baseline diameter ranging from 2.4 to 3.1 mm along the length of the implant (based on on-line QCA analysis) were selected, and the implantation pressure was varied according to the balloon compliance curve to achieve a stent/vessel ratio of 1.1:1 to 1.2:1. Repeat angiograms were conducted just prior to euthanasia and vessel harvest. QCA analysis was performed. All animals were pretreated with 325 mg aspirin, 75 mg clopidogrel, and amiodarone 75 mg daily for 3 days prior to the day of the procedure. All animals were post-treated with aspirin 325 mg and clopidogrel 75 mg p.o. daily until termination.

Angiographic Analysis

Angiograms were performed at the time of the initial catheterization and at 30 days of follow up. Quantitative Coronary angiography was performed (GE medical systems). Typical measures of angiographic neointimal formation were measured including reference vessel diameter, balloon to artery ratio, minimal luminal diameter (MLD), late loss (LL), and percent diameter of stenosis. LL is defined as MLD follow-up − MLD baseline. Percent Diameter stenosis is defined as the follow-up average reference vessel diameter (mean 5-mm diameter proximal to stent + mean 5-mm distal to stent/2) − MLD follow up, all divided by follow up average reference vessel diameter.

Histomorphometric Analysis

After euthanasia of the pig, coronary arteries were perfusion fixed at 100–120 mm Hg with ~500 ml of formalin. After overnight immersion–fixation, the hearts were sent to the CV Path, International Registry of Pathology. The stented vessel segments were dehydrated in a graded series of ethanol and embedded in methylmethacylate plastic. After polymerization, 2–3 mm sections were sawed from the proximal, mid, and distal portions of each single stent. Sections from the stents were cut on a rotary microtome at 4–5 μm, mounted and stained with hematoxylin and eosin and elastic Van Gieson stains. Segments of the native coronary arteries proximal and distal to the stents were taken for paraffin histology. Sections of the vessels were cut on a rotary microtome at 4–5 μm, mounted and stained with hematoxylin and eosin and Movat pentachrome stains. All sections were examined by light microcopy for the presence of inflammation, thrombus, neointimal formation, and vessel wall injury. Myocardial sections were taken from the anterior, lateral, posterior, and septal walls of the left ventricle distal to the sent and from the apical region of the left ventricle and examined for the presence of infarct, thromboembolus, and inflammation. To determine localized affects of the drug, the myocardium was also sampled beneath the area of stent placement. Histomorphometric analysis was performed including vessel injury score (Schwartz method), cross sectional areas (external elastic lamina [EEL], internal elastic lamina [IEL] and lumen), neointimal thickness, percent stenosis, neointimal inflammation, adventitial inflammation, fibrin coverage, and percent endothelialization. Neointimal thickness was measured as the distance from the inner surface of each stent strut to the luminal border. Area measurements were used to calculate vessel layer areas with the following formulas: Media = EEL − IEL, Neointima = IEL − Lumen, and % Stenosis = 100 × (Neointimal Area/IEL). Ordinal data were collected on each stent section and included strut apposition to the vessel wall, fibrin deposition, granuloma reactions, and hemorrhage around the stent struts and were expressed as a percentage of the total number of struts in each section. An overall neointimal inflammation, adventitial inflammation, and fibrin score were measured for each section. For neointimal inflammation, a score of 0 is less than 25% of struts with fewer than 10 inflammatory cells, a score of 1 is up to 25% of struts with greater than 10 inflammatory cells, a score of 2 is 25–50% of struts with greater

TABLE I. Summary of Vessel Injury

Stent type	Balloon/artery ratio	Injury score
Bare metal	1.19 ± 0.04	0.77 ± 0.46
Pimecrolimus slow release	1.18 ± 0.07	0.62 ± 0.26
Pimecrolimus fast release	1.21 ± 0.08	0.47 ± 0.38

$P = 0.22$ when comparing injury scores between groups (ANOVA).
$P = 0.60$ when comparing *B/A* ratio between all groups (ANOVA).

than 10 inflammatory cells, a score of 3 is greater than 50% of struts with greater than 10 inflammatory cells, and a score of 4 is two or more struts with granulomatous inflammatory reactions. A fibrin score of 0 is absent to focal residual fibrin involving any portion of the artery, a score of 1 is mild fibrin deposition involving less than 10% of the circumference of the artery or around less than 25% of the stent struts, a score of 2 is moderate fibrin deposition involving 10–25% of the circumference of the artery or around 25–50% of the stent struts, and a fibrin score of 3 is heavy deposition of fibrin involving greater than 25% of the circumference of the artery or surrounding greater than 50% of the stent struts. Adventitial inflammation was scored a 0 for no inflammation to minimal interspersed inflammatory cells anywhere in the adventitia, a 1 for mild peripheral inflammatory infiltration or focally marked in less then 25% of adventitial area, a 2 for moderate peripheral inflammatory infiltration or focally marked in 25–50% of adventitial area, and a 3 for heavy peripheral inflammatory infiltration or focally marked in greater than 50% of adventitial area. Endothelial coverage was semi quantified and was assessed microscopically on 6-μm sections stained with hematoxylin and eosin. The artery was divided into quadrants as a guide, and percent coverage is reported based on total luminal circumference.

Statistical Analysis

Angiographic and histological data were analyzed by comparing control and pimecrolimus eluting stents and control and combination drug stents by use of a one way ANOVA and Student's *t*-test. When ANOVA was used for multiple groups, pair-wise comparisons involving the control and different treatment groups were performed according to the post hoc Dunnett test. The level of significance was taken as $P < 0.05$. Results are reported as mean ± SD. All statistics were calculated with SPSS software.

RESULTS

Phase One: Pimecrolimus Study

There were ten pigs that each received three single stents deployed in the LAD, LCX, and RCA. The animals received 30 stents in a total of 30 coronary arteries (10 stents in each group [bare metal control, fast-release pimecrolimus, and slow-release pimecrolimus]). All pigs survived to completion of the 30-day study without evidence of myocardial infarction on gross inspection. No myocardial changes of ischemia or healed infarction were observed in any of the animals. The myocardium appeared healthy without changes of myocardial necrosis or fibrosis. Twenty-nine stents were analyzed. One of the slow-release pimecrolimus stents was not included in the QCA or histomorphometric analysis. Histologic analysis showed that the lumen was totally occluded by acute thrombus. There was no significant difference in injury between the three groups as seen by the similarity in the balloon to artery ratio and injury scores (Table I).

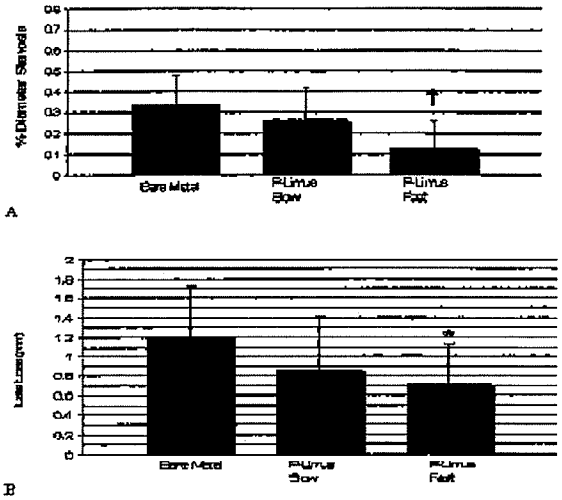

Fig. 2. A: Percent diameter stenosis versus stent type. B: Late loss versus stent type. †$P = 0.004$ versus control (Dunnettt's Test). *$P = 0.07$ versus control (Dunnettt's test).

Angiographic Analysis

The angiograms of the pimecrolimus treated pigs showed a reduction in neointimal formation when compared with the bare metal controls. Angiograms were evaluated for LL and percent diameter stenosis at 30-day follow up (Fig. 2). There was a near-significant trend toward decreased LL in the fast release pimecrolimus treated group, with the bare metal stent having a LL of 1.20 ± 0.52, and the fast release pimecrolimus group having a LL of 0.71 ± 0.43 ($P = 0.07$ by Dunnett's test). There was a similar trend seen in percent diameter stenosis, with statistical significance seen between the bare metal group (34% ± 14%) and the fast release pimecrolimus group (13% ± 13%, $P = 0.004$ by Dunnett's test). Although there was a trend

towards decreased LL (0.86 ± 0.55) and percent diameter stenosis (26% ± 15%) in the slow release pimecrolimus group, there was no statistically significant difference as compared with the bare metal control.

Histomorphometric Analysis

Arterial cross sections of the different stent groups are shown in Fig. 3. On gross inspection, a decrease in neointimal formation in the slow and fast release pimecrolimus groups is seen when compared with control. The histomorphometry data for each of the stent groups are summarized in Table II and Fig. 4. In terms of efficacy, there was significantly less neointimal thickness in the fast release pimecrolimus group as compared with bare metal stent ($P = 0.02$ by Dunnett's), while statistical significance was not seen between the slow release pimecrolimus and controls ($P = 0.10$ by Dunnett's). A regression analysis of strut injury versus neointimal thickness was also performed. This demonstrated a significant reduction of neointimal thickness for both pimecrolimus groups as compared with control and no significant difference between the two treatment groups (Fig. 5). There was significantly less neointimal inflammation ($P = 0.004$ by ANOVA) and adventitial inflammation ($P = 0.005$ by ANOVA) in both pimecrolimus groups as compared bare metal controls. To evaluate stent healing, intimal fibrin scores and percent endothelialization of the lumen were measured. Fibrins scores and percent endothelialization showed no statistically significant difference across all groups (see Table II).

Fig. 3. Coronary artery morphology 30 days after stent placement. All arteries are from the same animal. Section A is from the RCA with a bare metal stent. Section B is from the LCX with a fast release pimecrolimus stent. Section C is from the LAD with a slow release pimecrolimus stent. Low power views (×2) show increased neointimal formation in the bare metal cross section (A) when compared with the pimecrolimus cross sections (B and C). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Phase 2: Dual Drug Study

Seven pigs each received three single stents deployed in the LAD, LCX, and RCA, except for the RCA of animal p5-47, which was too small for implantation. The animals received twenty stents in a total of twenty coronary arteries (12 stents in dual drug group, 8 stents in the bare metal control group). All pigs, except for animal p5-43, survived to completion of the 30-day study. Animal p5-43 died after 2 weeks after stent implantation. Gross inspection revealed aneurismal dilation around the LAD stent, which was confirmed by light microscopy to be a healing medial dissection, which occurred at the time of initial implantation as evidenced on angiography. The rest of the animals were without evidence of myocardial infarction on gross inspection. No myocardial changes of ischemia or healed infarction were observed in any of the animals. The myocardium appeared healthy without changes of myocardial necrosis or fibrosis. A total of 17 stents were analyzed by quantitative angiography and histomorphometry (10 dual drug stents and 7 bare controls). There was no significant difference in injury between the three groups as seen by the similarity in the balloon to artery ratio and injury scores (Table III).

Angiographic Analysis

The angiograms of the dual-drug treated pigs showed a reduction in neointimal formation when compared with the bare metal controls. Angiograms were evaluated for LL and percent diameter stenosis at 30-day follow up (Fig. 6). There was a statistically significant decrease in LL in the dual drug treated group as compared with the bare metal group (0.26 ± 0.15 vs. 0.94 ± 0.40, $P = 0.003$ by t-test). There was a similar significant decrease in percent diameter stenosis, with statistical significance seen between the bare metal group (28% ± 15%) and the dual drug group (8% ± 5%, $P = 0.01$ by t-test).

TABLE II. Summary of Histologic Markers of Vessel Healing at 30 Days

Stent type	% Endothelialization	Neointimal inflammation score	Adventitial inflammation score	Fibrin score
Bare metal	98.67 ± 2.69	1.40 ± 1.09	0.87 ± 1.00	0.63 ± 0.71
Pimecrolimus slow release	97.80 ± 2.99	0.33 ± 0.58[a]	0.07 ± 0.15[b]	0.70 ± 0.51
Pimecrolimus fast release	98.67 ± 2.09	0.27 ± 0.41[c]	0.00 ± 0.00[d]	0.70 ± 0.94

$P = 0.66$ for % endothelialization between all groups (ANOVA).
$P = 0.97$ for fibrin score between all groups (ANOVA).
[a]$P = 0.009$ vs. control (Dunnett's).
[b]$P = 0.004$ vs. control (Dunnett's).
[c]$P = 0.01$ vs. control (Dunnett's)
[d]$P = 0.006$ vs. control (Dunnett's).

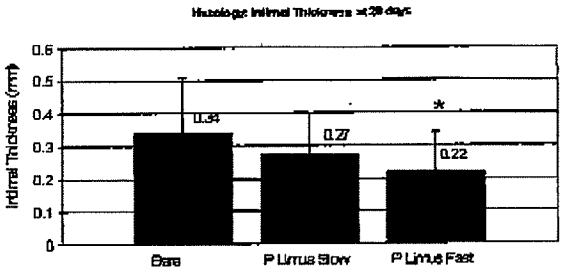

Fig. 4. Intimal thickness at 28 days. *P = 0.02 versus control (Dunnett's Test).

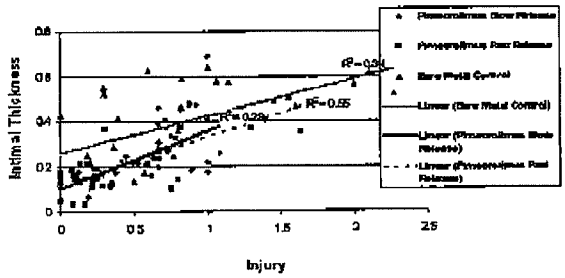

Fig. 5. Regression analysis of injury versus intimal thickness. For each given amount of injury, both slow release and fast release pimecrolimus show lower neointimal thickness as compared with bare control.

Histomorphometric Analysis

Arterial cross sections of the different stent groups are show in Fig. 7. On gross inspection, a decrease in neointimal formation in the dual drug group is seen when compared with the bare metal control group. The histomorphometry data for each of the stent groups are summarized in Table IV and Fig. 8. In terms of efficacy, there was significantly less neointimal thickness in the dual drug group as compared with bare metal stent (0.16 ± 0.07 vs. 0.33 ± 0.18, $P = 0.01$). Neointimal inflammation was similar between the dual drug and control stents (0.57 ± 0.57 vs. 0.48 ± 0.47, $P = 0.73$) and no significant adventitial inflammation was seen in either group. To evaluate stent healing, intimal fibrin scores and percent endothelialization of the lumen were measured. Percent endothelialization showed no statistically significant difference between the dual drug and control stents ($93\% \pm 10\%$ vs. $98\% \pm 2\%$, $P = 0.22$). There was greater neointimal fibrin seen in the dual drug stents as compared with the bare metal stents (1.23 ± 0.32 vs. 0.36 ± 0.34, $P = 0.0001$).

DISCUSSION

This proof of concept study is significant in several respects. First, in this porcine model, we have demonstrated the efficacy of a pimecrolimus drug eluting stent. This establishes pimecrolimus as a potential new therapeutic agent for drug eluting stents. Second, since pimecrolimus has no direct anti-proliferative properties, these data may have important implications with respect to mechanisms of poststent intimal hyperplasia. If borne out in human studies, the efficacy of pimecrolimus would tend to support the role of inflammation as central to the biologic response to stent injury as proposed by some investigators [17–23]. Second, to the best of our knowledge, this is the first study to describe simultaneous sustained release of dual agents from a stent with independent programmable release kinetics. This development establishes the framework for a wide variety of potential new therapeutic combinations. Finally, we did show both safety and efficacy with this dual drug eluting stent in this porcine model, but we failed to show superiority as compared with the pimecrolimus only stent configuration, despite our hypothesis that we expected a synergistic superiority of the dual drug eluting stent.

In the first phase of the study we examined the safety and efficacy of a pimecrolimus drug eluting

TABLE III. Summary of Vessel Injury

Stent type	Balloon/artery ratio	Injury score
Bare metal	1.18 ± 0.06	0.47 ± 0.29
Pimecrolimus/paclitaxel combination stent	1.21 ± 0.10	0.37 ± 0.17

$P = 0.41$ when comparing injury scores between groups (ANOVA).
$P = 0.37$ when comparing B/A ratio between all groups (t-test).

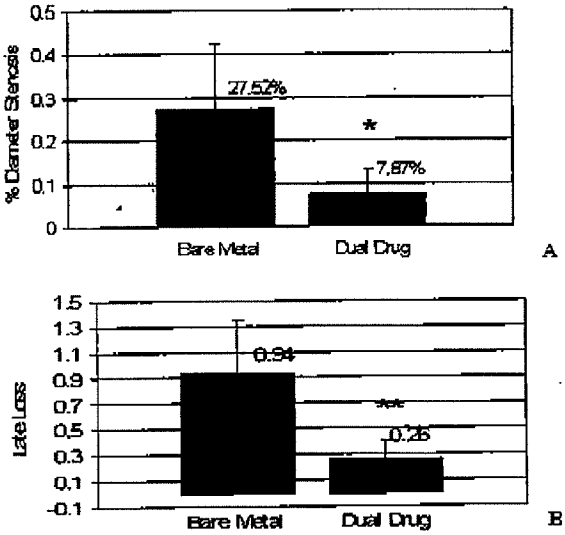

Fig. 6. A: Percent diameter stenosis versus stent type. B: Late loss versus stent type. *P = 0.01 versus control (t-test). **P = 0.003 versus control (t-test).

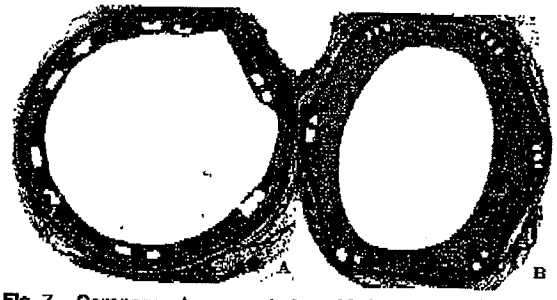

Fig. 7. Coronary artery morphology 30 days after stent placement. Section A is from the LAD with a paclitaxel/pimecrolimus combination stent. Section B is from the LAD with a bare metal stent. Low power views (×2) show increased neointimal formation in the bare metal cross section (B) when compared with the dual drug eluting stent (A). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

TABLE IV. Summary of Histologic Markers of Vessel Healing at 30 Days

Stent type	% Endothelialization	Neointimal inflammation score	Fibrin score
Bare metal	98.67 ± 2.69	0.48 ± 0.47	0.36 ± 0.34
Dual drug stent	97.80 ± 2.99	0.57 ± 0.57	1.23 ± 0.32[a]

$P = 0.22$ for % endothelialization between groups (ANOVA).
$P = 0.73$ for neointimal inflammation score between groups.
[a] $P < 0.0001$ (ANOVA) dual vs. bare for fibrin score between groups.
There was no significant adventitial inflammation in either group.

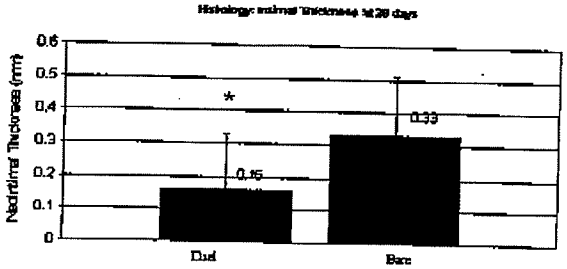

Fig. 8. Neointimal thickness at 28 days between dual drug eluting stents and bare metal controls. *$P = 0.014$ (ANOVA).

stent. On overall quantitative analysis of histologic sections the fast release pimecrolimus formulation appeared to be more effective than the slower one. This difference appeared to disappear with regression analysis comparing intimal thickness corrected for variation in strut injury. The porcine model is known to be injury dependent [24]. Whether a larger study would bring out clearer differences between the two formulation groups is unknown. Both groups demonstrated reduction in vascular inflammation as compared with bare metal stents. Both pimecrolimus formulations resulted in excellent vascular healing as demonstrated by a lack of excessive intimal fibrin and completed endothelialization by 30 days. Since pimecrolimus does not directly effect cell proliferation, the finding that pimecrolimus did not inhibit endothelial regeneration is not unexpected.

Other anti-inflammatory agents such as dexamethasone have been tried without success as coatings of drug eluting stents [25–27]. One might question why corticosteroids were ineffective while pimecrolimus was effective in the present study. These drugs work by markedly different mechanisms. Steroids act by much broader immunosuppressive effects at the level of the nucleus. They inhibit all known cytokines, inhibit cell migration of neutrophils, eosinophils, and macrophages, inhibit production of cox-2, and cause a rapid depletion of circulating T-cells [28–34]. As noted previously, pimecrolimus acts primarily as a calcineurin inhibitor and therefore mainly interferes with the synthesis of IL-2. This difference of a broad versus narrow spectrum of immunosuppressive response may be important in the modulation of the pathways responsible for stent induced intimal proliferation.

In the second phase of the study we examined the safety and efficacy of a combination drug eluting stent. This dual stent showed less neointimal formation by quantitative angiography and by histomorphometry as compared with the bare metal stents. Anecdotally, the neointimal thickness of the dual drug stent appeared to be less than previously shown with even 30 μg of paclitaxel in our laboratory, although no conclusions with respect to enhanced inhibitory effects versus paclitaxel alone may be drawn since we did not perform direct comparison in the present study [7]. The dual drug stents showed no significant difference in inflammation as compared with bare metal stents. This may be the result of the halved dose of pimecrolimus used as compared with the pimecrolimus alone study or to the presence of paclitaxel, which even at low doses may produce subtle inflammatory findings [7,22,35].

With respect to arterial healing, endothelialization was near complete in both the dual drug group and the bare metal group. There was no statistically significant difference between the groups. Unlike the pimecrolimus only stents, the dual drug stents did show a statistically significant increase in neointimal fibrin formation as compared with the bare metal controls. This increased intimal fibrin is likely due to the addition of paclitaxel to the stent. Intimal fibrin is a marker for overall stent healing, and one does expect delayed stent healing with paclitaxel [7,35].

Besides showing safety and efficacy in the dual drug eluting stent analysis, the second goal of that study was to see a synergistic decrease in neointimal formation with the dual drug eluting stent compared with the pimecrolimus stent. While there was a trend

towards decreased neointimal thickness (0.16 ± 0.07 in the dual drug group compared with 0.22 ± 0.13 in the fast release pimecrolimus group), this was not statistically significant. Therefore, we were unable to prove this hypothesis. It is possible with a larger sample size, we might have seen a statistically significant difference. We were also hampered by manufacturing constraints at the time to only use half the dose of pimecrolimus (162 μg) on the dual drug eluting stent as compared with that used in the pimecrolimus only study. This decreased dose of pimecrolimus was likely not as effective at decreasing inflammation as the full 325 μg dose was.

The possibilities for dual drug stents are intriguing. In the present case the agents were directed at inhibition of neointimal formation. One can easily imagine combinations with other therapeutic goals. For example, combining an anti-proliferative or anti-inflammatory with a PPAR agonist in diabetics, combining an anti-proliferative with an anti-thrombotic, or combining an anti-proliferative with an agent to promote myocardial salvage and/or regeneration following myocardial infarction may one day be possible.

The present study is subject to limitations. It was designed as a proof of concept for a novel agent with specific anti-inflammatory effects and for dual agents. It is not intended as a definitive preclinical evaluation. Any consideration for clinical trial would necessarily include more animals with control groups of polymer only stents as well as those with each of the two drugs alone. Follow-up at both 30 and 90 days would be required so as to assure no deleterious long-term findings. This not withstanding, the present polymers have been demonstrated as safe in both long-term animal and human studies [7,16,36]. As such, the probability of significant and unpredictable adverse effects at 90 days seems diminished. The porcine model is best suited for determination of safety. Relative human efficacy is less predictable in this model and can only be definitively ascertained in clinical trials [37].

CONCLUSION

In conclusion, this study demonstrated that in a 30-day porcine stent model, pimecrolimus inhibits neointimal proliferation as compared with bare metal stents. Pimecrolimus, currently approved for the treatment of atopic skin disorders, is worthy of further study as a potential agent for use in drug eluting stents. The concept of sustained dual drug delivery from stents is established. The possibility of combination therapy for improving the safety and efficacy of drug eluting stents as well as expanding their indications is worthy of further research and development.

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Catheterization and Cardiovascular Interventions DOI 10.1002/ccd.
Published on behalf of The Society for Cardiovascular Angiography and Interventions (SCAI).

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Journal of the American College of Cardiology (ISSN 0735-1097) is issued monthly, except semimonthly in March and November, in two indexed volumes per year by Elsevier Science Inc., 655 Avenue of the Americas, New York, NY 10010. Printed in USA at 500 Cadmus Lane, Easton, MD 21601-0969. Subscription prices per year: For customers in the USA only: institutional rate: US$ 214.00, personal rate: US$ 140.00, student/resident rate: US$ 86.00. For surface mail delivery to customers in Europe, The CIS, and Japan: institutional rate: NLG 501.00, personal rate: NLG 381.00, student/resident rate: NLG 284.00. For air mail delivery to customers in Europe and The CIS: institutional rate: NLG 696.00, personal rate: NLG 576.00, student/resident rate: NLG 489.00. For air mail delivery to customers in Europe and The CIS: institutional rate: NLG 1027.00, personal rate: NLG 907.00, student/resident rate: NLG 820.00. For surface airlift to customers in Japan: institutional rate: NLG 809.00, personal rate: NLG 689.00, student/resident rate: NLG 602.00. For air mail delivery to customers in Japan: institutional rate: NLG 1027.00, personal rate: NLG 907.00, student/resident rate: NLG 820.00. For surface delivery to customers in all other countries: institutional rate: US$ 309.00, personal rate, US$ 235.00, student/resident rate: US$ 181.00. For air mail delivery to customers in all other countries: institutional rate: US$ 384.00, personal rate: US$ 310.00, student/resident rate: US$ 256.00. Prices include postage and are subject to change without notice. Periodicals postage paid at New York, NY and at additional mailing offices. Postmaster: Send address changes to *Journal of the American College of Cardiology*, Elsevier Science Inc., 655 Avenue of the Americas, New York, NY 10010.

0735-1097(199710)30:4;1-D

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Effect of Pravastatin on Angiographic Restenosis After Coronary Balloon Angioplasty

MICHEL E. BERTRAND, MD, FACC, EUGÈNE P. McFADDEN, MRCP, FACC, JEAN-CHARLES FRUCHART, PhD, ERIC VAN BELLE, MD, PHILIPPE COMMEAU, MD,* GILLES GROLLIER, MD,† JEAN-PIERRE BASSAND, MD,‡ JACQUES MACHECOURT, MD,§ JEAN CASSAGNES, MD,‖ JEAN-MARIE MOSSARD, MD,¶ ANDRÉ VACHERON, MD,# ALAIN CASTAIGNE, MD,** NICOLAS DANCHIN, MD, FACC,†† JEAN-MARC LABLANCHE, MD, FACC, FOR THE PREDICT TRIAL INVESTIGATORS‡‡

Lille, Caen, Besançon, Grenoble, Clermont-Ferrand, Strasbourg, Paris, Creteil and Nancy, France

Objectives. This study sought to determine whether pravastatin affects clinical or angiographic restenosis after coronary balloon angioplasty.

Background. Experimental data and preliminary clinical studies suggest that lipid-lowering drugs might have a beneficial effect on restenosis after coronary angioplasty.

Methods. In a multicenter, randomized, double-blind trial, 695 patients were randomized to receive pravastatin (40 mg/day) or placebo for 6 months after successful balloon angioplasty. All patients received aspirin (100 mg/day). The primary angiographic end point was minimal lumen diameter (MLD) at follow-up, assessed by quantitative coronary angiography. A sample size of 313 patients per group was required to demonstrate a difference of 0.13 mm in MLD between groups (allowing for a two-tailed alpha error of 0.05 and a beta error of 0.20). To allow for incomplete angiographic follow-up (estimated lost to follow-up rate of 10%), 690 randomized patients were required. Secondary end points were angiographic restenosis rate (restenosis assessed as a categoric variable, >50% stenosis) and clinical events (death, myocardial infarction, target vessel revascularization).

Results. At baseline, clinical, demographic, angiographic and lipid variables did not differ significantly between groups. In patients treated with pravastatin, there was a significant reduction in total and low density lipoprotein cholesterol and triglyceride levels and a significant increase in high density lipoprotein cholesterol levels. At follow-up the MLD (mean ± SD) was 1.47 ± 0.62 mm in the placebo group and 1.54 ± 0.66 mm in the pravastatin group ($p = 0.21$). Similarly, late loss and net gain did not differ significantly between groups. The restenosis rate (recurrence >50% stenosis) was 43.8% in the placebo group and 39.2% in the pravastatin group ($p = 0.26$). Clinical restenosis did not differ significantly between groups.

Conclusions. Although pravastatin has documented efficacy in reducing clinical events and angiographic disease progression in patients with coronary atherosclerosis, this study shows that it has no effect on angiographic outcome at the target site 6 months after coronary angioplasty.

(J Am Coll Cardiol 1997;30:863–9)

Over the past 15 years, it has becoming increasingly evident that percutaneous transluminal coronary angioplasty (PTCA) is an effective method of myocardial revascularization. Compared with medical treatment in patients with left anterior descending coronary artery stenosis, PTCA has demonstrated its superiority in terms of decreasing symptoms and improving exercise performance (1). Six multicenter randomized trials comparing PTCA with coronary artery bypass graft surgery (CABG) have shown that survival without myocardial infarction was similar for the two treatment modalities (2–9). However, patients treated by PTCA had more revascularization procedures than patients treated by CABG, mainly related to the occurrence of restenosis. This phenomenon remains the Achilles' heel of PTCA. Restenosis is relatively frequent, occurring in 35% to 40% of dilated lesions, is often associated with recurrence of symptoms requiring further revascularization and has a major economic impact. The mechanisms of restenosis have been extensively studied, and four major mechanisms have been identified: immediate recoil, incorporation of thrombus and a healing process in response to arterial injury that involves myointimal proliferation and vascular remodeling.

When the present study was designed, myointimal proliferation was considered to play a dominant role in the pathogen-

From the Division of Cardiology B, Hopital Cardiologique, Lille; *Clinique St. Martin, Caen; and Centres Hospitalier Universitaire, †Caen, ‡Besançon, §Grenoble, ‖Clermont-Ferrand, ¶Strasbourg, #Necker (Paris), **Creteil and ††Nancy, France. ‡‡A list of participating centers and principal investigators for the PREDICT Trial appears in the Appendix. This study was supported by a grant from Bristol Myers Squibb Laboratories, Paris.

Manuscript received January 6, 1997; revised manuscript received June 17, 1997, accepted June 26, 1997.

Address for correspondence: Dr. Michel E. Bertrand, Division of Cardiology B, Hôpital Cardiologique, Boulevard du Professeur Leclercq, 59037 Lille, France. E-mail: bertrandmc@AOL.com.

Published by Elsevier Science Inc.

0735-1097/97/$17.00
PII S0735-1097(97)00259-3

Abbreviations and Acronyms

CABG	= coronary artery bypass graft surgery
CARE	= Cholesterol and Recurrent Events (trial)
CAESAR	= Computer-Assisted Evaluation of Stenosis and Restenosis system
HDL	= high density lipoprotein
LDL	= low density lipoprotein
Lp(a)	= lipoprotein(a)
LRT	= Lovastatin Restenosis Trial
MLD	= minimal lumen diameter
PREDICT	= Prevention of Restenosis by Elisor After Transluminal Coronary Angioplasty (trial)
PTCA	= percutaneous transluminal coronary angioplasty

esis of restenosis. Furthermore, several lines of evidence suggested that the phenomenon of restenosis and that of atherosclerosis progression had some pathophysiologic characteristics in common. Several angiographic studies had described less progression and even some regression of atherosclerosis when lipid levels were lowered (10,11). In addition, experimental and clinical data showed a trend toward a lower restenosis rate when patients undergoing PTCA received fish oil supplementation (12–17). In this context, the Prévention des Restenoses par Elisor après Dilatation Coronaire Transluminale (Prevention of Restenosis by Elisor After Transluminal Coronary Angioplasty [PREDICT]) study* was designed to determine whether treatment with pravastatin, an HMG coenzyme A reductase inhibitor, was able to reduce restenosis after PTCA.

Methods

Study design. From 1992 to 1994, 695 patients were enrolled in this prospective multicenter, randomized, double-blind, placebo-controlled trial. The protocol was approved by the ethics committee of the University of Lille. The last angiographic follow-up procedure was performed in December 1994. Twenty-nine French centers (see Appendix) participated in the study.

Patients 25 to 75 years old, with a left ventricular ejection fraction, assessed by angiography, that exceeded 40% were eligible for inclusion. In addition, all patients were required to have total cholesterol levels between 200 and 310 mg/dl and triglyceride levels <500 mg/dl. Patients with a recent myocardial infarction (within 15 days) and patients who had previously undergone PTCA or CABG of the target vessel were excluded. Patients were also excluded if they received drugs not allowed by protocol (fish oil or other lipid-lowering agents within 1 month of the procedure), corticosteroids or immunosuppressive drugs.

Patients were recruited from those who had undergone successful, uncomplicated PTCA of one or more coronary stenoses in the participating institutions. Randomization was performed after PTCA and within 24 h of the procedure. After giving written informed consent, patients were randomly assigned to receive either pravastatin (40 mg/day) or placebo. All patients received aspirin (100 mg/day).

Two months after the procedure, patients returned for outpatient assessment and blood sampling for lipid measurements. At 6-month follow-up, lipid measurements and coronary angiography were performed. Follow-up angiography was performed earlier if there was a clinical indication. If follow-up angiography performed <4 months did not demonstrate restenosis, the patient was encouraged to return for further angiography at 6 months.

Lipid measurements. The following measurements were performed at baseline and at 2 and 6 months: total, low density lipoprotein (LDL), high density lipoprotein (HDL) and HDL subfraction E (HDL-E) cholesterol; triglycerides; lipoprotein(a) [Lp(a)]; lipoprotein E-B; and apolipoprotein A1 and B.

All lipid measurements were performed at a core laboratory (Service d'Etude et de Recherche sur les Lipoproteines et l'Atherosclerose [SERLIA], J. C. Fruchart, PhD, Institut Pasteur, Lille, Director). The technicians performing the measurements were unaware of the treatment allocation.

Angiographic measurements. Catheterization and PTCA were performed according to standard techniques. Isosorbide dinitrate (2 mg) was injected into the coronary artery before each angiogram in an attempt to standardize vasomotor tone. The angiograms were recorded on standard 35-mm film. Three views of the stenosis were obtained at the time of PTCA and were recorded on a worksheet to allow them to be duplicated exactly at the time of follow-up angiography. An attempt was made to obtain two orthogonal views for each lesion.

At the end of the study, films were sent to the core laboratory at the University of Lille (J. M. Lablanche, MD and E. McFadden, Directors) for qualitative and quantitative analysis. Angiographic analysis was performed without knowledge of treatment allocation or of clinical data. Quantitative analysis was performed on sequential angiograms filmed in the same projection. The frames were selected by the cardiologist who performed the quantitative analysis from the projection in which the stenosis appeared most severe just before angioplasty. Quantitative analysis was performed with the Computer-Assisted Evaluation of Stenosis and Restenosis (CAESAR) system, a computerized automatic analysis system that has been described in detail elsewhere (18). Briefly, the 35-mm cine film was projected with a 35AX projector (Tagarno, Denmark), and the cine frame selected for analysis was scanned with a high resolution video camera. The signal produced by the video camera was digitized and displayed on a video monitor. Regions of interest were chosen in the vessel, and a centerline was manually traced with use of a light pencil. The contours of the vessel were then automatically detected on the basis of the weighted sum of first- and second-derivative functions applied to the digitized brightness information. The diameter of the empty coronary catheter was used to convert the imaging data from pixels to millimeters. The mean diam-

*Elisor is the registered trade name of Pravastatin.

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eters of proximal and distal reference segments and the minimal diameter of the stenotic segment were measured. The accuracy (defined as the signed difference between the measured and the true value) and the precision (defined as the standard deviation of these differences) of the CAESAR system were previously determined in a study analyzing cine films of Plexiglas blocks containing precision-drilled models of coronary arteries filled with contrast medium. The accuracy was 0.07 mm and the precision 0.14 mm. To assess the intraobserver and interobserver variability of the system, 90 arterial segments from patients undergoing PTCA were analyzed by two independent observers (J.M.L., E.P.M.) and reanalyzed at a remote time. The mean intraobserver variation, expressed as the standard deviation of the differences, was 0.10 mm, and the interobserver variation was 0.11 mm.

End points. Predetermined clinical and angiographic end points were assessed. The primary angiographic end points were minimal lumen diameter (MLD) at follow-up angiography, net gain and late loss in MLD at the dilated site. When more than one lesion was dilated in the same patient, the first lesion dilated was used for assessment of the primary angiographic end point. Secondary end points were the percent of patients with recurrence >50% stenosis at follow-up (at any dilated lesion) and the following clinical end points: occurrence of death, nonfatal target lesion myocardial infarction, CABG or repeat PTCA of the target lesion. Target lesion myocardial infarction was defined clinically at the participating site. These clinical end points constitute clinical restenosis.

Definitions. *Acute gain* was defined as the MLD at the dilated site immediately after PTCA minus the MLD just before the procedure. *Late loss* was defined as the MLD at the dilated site immediately after the procedure minus the MLD at the dilated site 6 months after PTCA. *Net gain* was defined as the MLD at the dilated site 6 months after angioplasty minus the MLD at the dilated site just before angioplasty. Angiographic results given at follow-up are those obtained at 6 months, or earlier in case of early restenosis.

Data management and statistical analysis. The study adhered to the European Guidelines for Good Clinical Research Practice. Data were prospectively recorded by the investigators at each site on case record forms and were monitored by clinical research associates before data entry. The forms were verified by range and consistency checks, with queries returned to the investigators for any missing or inconsistent data. Clinical safety of the study drugs was evaluated, and adverse events occurring during the study were recorded in the case record form. At each center, research assistants monitored patient compliance with assigned therapy.

Statistical analysis was performed with use of SAS PC software (Version 6.04, SAS Institute). All tests were two-tailed, and p values <0.05 were considered significant. The predetermined primary end point of the study was the MLD at the dilated site 6 months after angioplasty. For this end point, it was calculated that a sample size of 313 patients/group was required to demonstrate a difference of 0.13 mm in MLD between the groups (allowing for a two-tailed alpha error of 0.05 and a beta error of 0.20). To allow for incomplete angiographic follow-up (estimated lost-to-follow-up rate of 10%), it was decided to randomize 690 patients. Two groups were defined: 1) all randomized patients (intention to treat group); 2) patients who had a follow-up angiogram that could be analyzed by the continuous MLD approach (per-protocol group) and who met angiographic criteria.

Baseline characteristics were compared in the two groups using the *t* test, chi-square test or Fischer exact test, as appropriate. Clinical events occurring during follow-up were compared with the Mantel-Haenszel test on ordered categories. When more than one clinical event occurred per patient, the most severe event was used for the analysis with the following decreasing order of severity: death, nonfatal myocardial infarction, CABG and target vessel repeat PTCA. MLD and changes in MLD and percent diameter stenosis (immediate gain, late loss and net gain) were compared between groups by *t* tests. Two-way analysis of variance was performed to test changes in lipid variables. Continuous variables are expressed as mean value ± SD.

Results

Patients. In total, 695 patients were randomized and make up the intention to treat cohort; 347 were assigned to pravastatin therapy and 348 to placebo. Because of adverse events (1 patient) and withdrawal of consent, 661 patients were seen at the 2-month follow-up visit. During subsequent follow-up, five patients had adverse events and stopped the treatment. Seventeen patients were lost to follow-up, and 14 refused the angiographic follow-up. In total, 625 patients (90% of the study group) had angiographic follow-up.

Taking into account patients excluded by the core laboratory (significant [>50%] residual stenosis after PTCA) or those unsuitable for quantitative analysis (n = 69), 556 patients (283 in the placebo group, 273 in the pravastatin group) were available for the per-protocol angiographic analysis. On average, the patients underwent follow-up angiography 184 ± 52 days after the procedure. There was no significant difference between the two groups (184 ± 55 days in the placebo group, 183 ± 47 days in the pravastatin group, p = 0.83).

Baseline clinical and angiographic characteristics. The two groups were well matched in terms of baseline clinical characteristics (Table 1). Mean age and the distribution of risk factors for coronary disease did not differ significantly between groups. The proportion of patients with a history of myocardial infarction was similar in both groups. A similar proportion of patients in both groups had stable angina or unstable angina (defined as severe chest pain at rest with electrocardiographic changes) or were asymptomatic.

The anatomic distribution and qualitative angiographic characteristics of the target lesions (assessed by the American College of Cardiology/American Heart Association classification) did not differ significantly between groups (Table 2).

Lipid measurements. At baseline, the mean cholesterol level was 231 ± 36 mg/dl in the placebo group and 228 ±

Table 1. Baseline Clinical Characteristics

	Placebo Group (n = 348)	Pravastatin Group (n = 347)	p Value
Mean age (yr)	58.5	58.2	NS
Range	32–75	31–75	
Male	289 (83%)	293 (84.4%)	0.61
Smoker	118 (34%)	116 (30.5%)	0.89
Hypertension	108 (31%)	105 (30.3%)	0.82
Diabetes	30 (8.6%)	20 (5.8%)	0.14
PVD	20 (5.7%)	13 (3.7%)	0.21
Hx of stroke	7 (2%)	6 (1.7%)	0.78
Previous MI	131 (37.6%)	127 (36.6%)	0.77
Stable angina	140 (40.2%)	142 (40.9%)	0.85
Unstable angina	62 (17.8%)	49 (14.1%)	0.18

Data presented are number (%) of patients, unless otherwise indicated. Hx = history; MI = myocardial infarction; PVD = peripheral vascular disease.

Table 2. Baseline Lesion Characteristics

	Placebo Group (n = 308)	Pravastatin Group (n = 299)	p Value
Lesion location			
RCA	92 (29.9%)	90 (30.1%)	0.95
LAD	126 (40.9%)	108 (36.1%)	0.22
LCx	90 (29.2%)	101 (33.8%)	0.22
Lesion type*			
A	159 (51.6%)	159 (53.2%)	0.70
B1	103 (33.4%)	107 (35.8%)	0.35
B2	44 (14.3%)	31 (10.3%)	0.14
C	2 (0.7%)	2 (0.7%)	0.97

*American College of Cardiology/American Heart Association/classification. Data presented are number (%) of patients. LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; RCA = right coronary artery.

38 mg/dl in the pravastatin group (p = 0.42). The mean level of LDL cholesterol was 157 ± 29 mg/dl in the placebo group and 155 ± 32 mg/dl in the pravastatin group (p = 0.3); mean HDL cholesterol was 47 ± 12 mg/dl in the placebo group and 47 ± 13 mg/dl in the pravastatin group (p = 0.8) (Table 3).

During the study there were no significant changes in lipid variables in the placebo group. In contrast, there was a significant decrease in mean total cholesterol in the pravastatin group after 2 and 6 months of treatment compared with the mean baseline value. Mean LDL cholesterol was also significantly lower at 2 and 6 months than at baseline. There was a significant increase in HDL cholesterol at 2 and 6 months compared with baseline values (Table 3). Apolipoprotein A1 significantly increased in the pravastatin group, whereas apolipoprotein B significantly decreased. Lp(a) levels were slightly but not significantly greater at 6 month follow-up (Table 4).

Angiographic results. The major results of the quantitative angiographic analysis are presented in Table 5. There were no significant differences at baseline in reference diameter or in MLD between groups. The MLD was 0.84 ± 0.28 mm in the placebo group and 0.82 ± 0.29 mm in the pravastatin group (p = 0.37).

At follow-up, the MLD, which was the primary angiographic end point, was 1.47 ± 0.62 mm in the placebo group and 1.54 ± 0.66 mm in the pravastatin group (p = 0.21). The cumulative distribution curves for MLD are shown in Figure 1. The late loss in MLD was similar in both groups (0.48 ± 0.56 mm in the placebo group, 0.46 ± 0.58 mm in the pravastatin group, p = 0.54), as was the net gain (0.62 ± 0.59 mm in the placebo group, 0.71 ± 0.62 mm in the pravastatin group, p = 0.07).

A secondary angiographic end point was percent stenosis. At baseline, mean stenosis severity at the PTCA site was similar (72 ± 8.8%) in the pravastatin and placebo groups (71.1 ± 8.1%, p = 0.11). After PTCA, mean residual stenosis was 33 ± 8.5% in the placebo group and 33 ± 8.5% in the pravastatin group (p = 0.49). At angiographic restudy, there was no significant difference between the two groups, with mean stenosis severity 49.7 ± 20% in the placebo group and 48.4 ± 20% in the pravastatin group (p = 0.44). Furthermore, the proportion of patients with recurrence of significant (>50%) stenosis did not differ significantly (p = 0.26) between groups (43.8% in the placebo group, 39.2% in the pravastatin group).

Clinical restenosis. The analysis, based on the intention to treat cohort, included 695 patients (348 in the placebo group, 347 in the pravastatin group). There were four deaths in the pravastatin group: two sudden deaths plus one related to myocardial infarction and one related to a cerebrovascular accident. One sudden death occurred in the placebo group. The mortality rate did not differ significantly between groups (p = 0.21).

Four nonfatal myocardial infarctions occurred in each group. Target vessel revascularization during follow-up was performed in 75 patients (21.6%) receiving placebo and 66 (19%) treated with pravastatin. Thus, there was no overall difference in clinical restenosis between the groups (Table 6).

Relation between lipid measurements and angiographic restenosis. There was no relation between late loss in MLD and changes in lipid variables associated with pravastatin treatment.

Discussion

The present study was designed to determine whether treatment with pravastatin could reduce angiographic restenosis after coronary balloon angioplasty. Angiographic restenosis was assessed using both a continuous approach (analysis of MLD) and a categoric approach (recurrence of significant [>50%] stenosis after initially successful PTCA). Both analyses demonstrated conclusively that pravastatin had no significant effect on angiographic restenosis.

Present study: clinical and angiographic outcome. Pravastatin treatment was associated with a significant reduction in total and LDL cholesterol and with a slight but significant increase in HDL cholesterol. However, pravastatin treatment had no significant effect on either angiographic restenosis or rate of clinical events after PTCA. The incidence of death,

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Table 3. Lipid Variables

	Placebo Group (mean ± SD)	No. of Pts	Pravastatin Group (mean ± SD)	No. of Pts	p Value
TC (mg/dl)					
Baseline	231 ± 36	347	228 ± 38	341	0.42
2 mo	247 ± 38	315	196 ± 34	320	0.0001
6 mo	239 ± 40	285	195 ± 37	288	0.0001
LDL-C (mg/dl)					
Baseline	157 ± 29	343	155 ± 32	338	0.3
2 mo	164 ± 33	311	119 ± 29	312	0.0001
6 mo	159 ± 33	283	119 ± 31	284	0.0001
HDL-C (mg/dl)					
Baseline	47 ± 12	345	47 ± 13	341	0.8
2 mo	51 ± 15	313	54 ± 13	317	0.001
6 mo	49 ± 14	286	52 ± 13	288	0.01
TG					
Baseline	139 ± 67	346	140 ± 75	341	0.8
2 mo	149 ± 91	315	126 ± 81	320	0.001
6 mo	159 ± 125	285	134 ± 88	288	0.01

HDL-C = high density lipoprotein cholesterol; LDL-C = low density lipoprotein cholesterol; Pts = patients; TC = total cholesterol; TG = triglycerides.

nonfatal myocardial infarction or target lesion revascularization was similar in both groups. The calculations of sample size were based on the number of patients required to demonstrate, with adequate power, an effect of treatment on angiographic restenosis after PTCA; a much larger sample size, as well as a longer period of follow-up, would be required to assess a potential effect on clinical outcome. Pravastatin did not reduce clinical restenosis in the present trial, but this finding is not at variance with the results of previous studies.

Statins and progression of atherosclerosis: previous studies. Previous studies that examined the effects of the statins on the occurrence of clinical events in patients with coronary atherosclerosis demonstrated a reduction in clinical events in patients receiving statin therapy. This benefit was observed in different populations and with different molecules, notably in the Scandinavian Simvastatin Survival Study (4-S) (19), the West of Scotland Coronary Prevention Study (WOSCOPS) (20) and the CARE study (21). In the 4S study, the actuarial survival curves diverged only after 12 months and in the CARE study after 2 years.

Several angiographic trials have found that lipid-lowering drugs were able to limit progression and even to induce regression of atherosclerotic lesions. This was demonstrated in the Regression Growth Evaluation Statin Study (REGRESS) study (11) that compared pravastatin with placebo over a longer time period. This question was not addressed in the PREDICT trial, which was designed to assess the effect of pravastatin on restenosis and not its effects on progression or regression in nondilated segments.

Lipid-lowering therapy: effects on restenosis. Previous studies that examined the effects of lipid-lowering drugs on restenosis have produced conflicting results. A potential ben-

Table 4. Lipoprotein Variables

	Placebo Group (mean ± SD)	No. of Pts	Pravastatin Group (mean ± SD)	No. of Pts	p Value
Apo A1 (mg/dl)					
Baseline	130.9 ± 25.7	347	133.5 ± 25.2	343	0.2
2 mo	146.4 ± 24.1	314	153.2 ± 25.7	320	0.006
6 mo	143.8 ± 27.6	282	150.5 ± 26.9	286	0.003
Apo B (mg/dl)					
Baseline	132.8 ± 25.7	348	131.1 ± 28.2	343	0.4
2 mo	148.1 ± 32.1	314	113.5 ± 29.1	320	0.0001
6 mo	143.1 ± 34.5	282	113.5 ± 32.4	286	0.0001
Lp(a) (mg/dl)					
Baseline	27.6 ± 33.6	346	27.2 ± 32.2	340	0.86
2 mo	28.6 ± 34.7	311	31.5 ± 38.3	315	0.33
6 mo	26.5 ± 30.6	276	32.1 ± 38.8	279	0.06

Apo = apolipoprotein; Lp = lipoprotein; Pts = patients.

Table 5. Angiographic Results

	Placebo Group (n = 283)	Pravastatin Group (n = 273)	p Value
Ref diam (mm)			
Before PTCA	3.04 ± 0.50	3.06 ± 0.45	0.65
After PTCA	3.04 ± 0.50	3.06 ± 0.45	0.63
At follow-up	3.04 ± 0.50	3.05 ± 0.45	0.82
MLD (mm)			
Before PTCA	0.84 ± 0.28	0.82 ± 0.29	0.37
After PTCA	1.95 ± 0.37	1.99 ± 0.39	0.18
At follow-up	1.47 ± 0.62	1.54 ± 0.66	0.21
Changes in MLD (mm)			
Acute gain	1.10 ± 0.34	1.17 ± 0.39	0.04
Late loss	0.48 ± 0.56	0.46 ± 0.58	0.54
Net gain	0.62 ± 0.59	0.71 ± 0.62	0.07
% stenosis			
Before PTCA	71.1 ± 8.1	72.2 ± 8.8	0.11
After PTCA	33.3 ± 8.56	32.8 ± 8.5	0.49
At follow-up	49.7 ± 19.8	48.4 ± 20	0.44

Data presented are mean value ± SD. MLD = minimal lumen diameter; PTCA = percutaneous transluminal coronary angioplasty; Ref diam = reference diameter.

Table 6. Clinical Events During Follow-Up

	Placebo Group (n = 348)	Pravastatin Group (n = 347)	p Value
Death	1 (0.3%)	4 (1.15%)	0.21
Acute MI	4 (1.1%)	4 (1.15%)	1.0
CABG	18 (5.2%)	15 (4.3%)	0.72
Repeat target lesion PTCA	57 (16.4%)	51 (14.7%)	0.54
Total	80 (23%)	74 (21.3%)	

Data presented are number (%) of patients. CABG = coronary artery bypass graft surgery; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.

eficial effect of the statins on the occurrence of restenosis was suggested by a relatively small study (22) that included 157 patients who received lovastatin or conventional care. That study (22), which was neither blinded nor randomized, reported that the rate of restenosis was 12% with lovastatin compared with 44% with conventional care; however, angiographic follow-up was incomplete. Subsequently, a small randomized trial (23) with pravastatin in a Japanese population demonstrated no effect on angiographic restenosis.

A large randomized trial, the Lovastatin Restenosis Trial (LRT) (24), examined the effect of lovastatin on restenosis. This well conducted and well designed study showed that treatment with a relatively high dose of lovastatin had no effect on the occurrence of restenosis at 6 months after PTCA. The results of the present study are similar to the results of the LRT. There were two methodologic differences between the studies, namely, the fact that in the LRT treatment was begun between 7 and 10 days before angioplasty, and the dose of statin used was higher (40 mg of lovastatin orally twice daily) compared with 40 mg/day of pravastatin in the present study. The population studied was somewhat larger in the PREDICT study (695 patients) than in in the LRT (404 patients). The reference diameters in the dilated vessels were slightly smaller in the LRT than in the PREDICT study, but the conclusions concerning the continuous and categoric variables were essentially the same. No trials to date have dealt with the effects of simvastatin or fluvastatin, statins that have been shown in vitro to have smooth muscle cell migration inhibitory properties on restenosis.

Other recent studies (25–27) have demonstrated a lack of association between serum lipid levels and restenosis and the lack of effect of lipid-lowering agents or fish oil supplementation on restenosis.

Conclusions. The results of the present study, together with those of the other studies discussed, demonstrate that despite its positive effects on the angiographic and ultrasound progression of atherosclerosis, pravastatin has no effect on

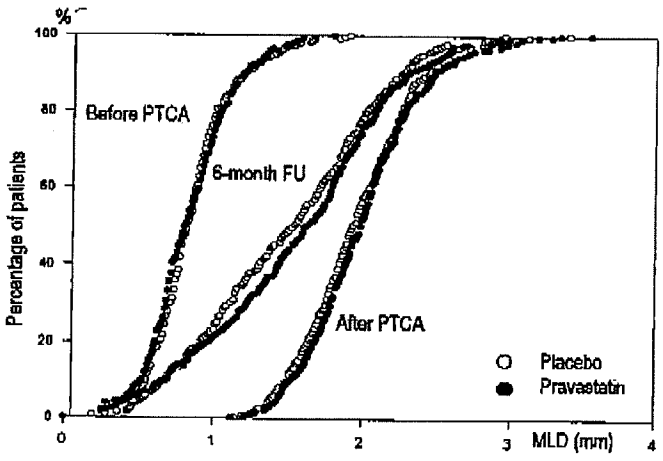

Figure 1. Cumulative distribution curves for MLD before and immediately after angioplasty and at follow-up (FU). The curves that are superimposed before angioplasty shift to the right after the procedure, reflecting the acute gain in MLD associated with the procedure. At follow-up, the curves shift back to the left because of the late loss in MLD during follow-up. The curves for pravastatin and placebo are essentially superimposed at all three timepoints, demonstrating the lack of effect of pravastatin.

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angiographic or clinical restenosis 6 months after coronary angioplasty despite a significant reduction in total and LDL cholesterol. These results should not be interpreted to mean that statin therapy is of no benefit in patients undergoing angioplasty. Although treatment with statins appears to have no effect on restenosis, their effect on the progression of atherosclerosis and on the clinical events associated with such progression now appears to have been established beyond reasonable doubt. Owing to the contrasting effects of lipid lowering on atherosclerosis and restenosis, it seems unlikely that restenosis and the progression of atherosclerosis have a similar pathophysiologic basis. Current evidence suggests that restenosis is related to an exaggerated healing process combined with vascular remodeling.

Appendix

*Participating Centers and Principal Investigators for the PREDICT Trial**

Clinique St. Martin, Caen (83): P. Commeau; *Centre Hospitalier Universitaire (CHU), Caen* (72): G. Grollier; *CHU, Besançon* (61): J. P. Bassand; *CHU, Grenoble* (49): J. Machecourt; *CHU, Clermont-Ferrand* (48): J. Cassagnes; *CHU, Strasbourg* (38): J. M. Mossard; *CHU Necker, Paris* (35): A. Vacheron, J. P. Metzger; *CHU, Creteil* (31): A. Castaigne; *CHU, Nancy* (30): N. Danchin; *CHU, Broussais, Paris* (27): J. L. Guermonprez, S. Makowski; *CHU, Lille* (26): M. Bertrand, C. Bauters; *CHU, Brest* (24): J. Boschat; *CHU Ambroise Paré, Paris* (21): J. P. Bourdarias; *Centre Hospitalier Régional, Mulhouse* (20): J. P. Monassier; *CHU, Amiens* (19): J. C. Quiret; *CHU, Tours* (16): P. Raynaud; *Institut Arnaud Tzanck, Nice* (15): R. Schmitt; *CHU, Nantes* (15): D. Crocher; *CHU, Rennes* (13): J. C. Pony, H. Le Breton; *CHU Timone, Marseille* (11): M. Bory; *CHU, Pitié Salpétrière, Paris* (11): G. Drobinski; *CHU, Rouen* (9): B. Letac; *CHU Bichat, Paris* (8): M. C. Aumont, D. Himbert; *CHU, Angers* (6): P. Geslin; *CHU, Dijon* (3): J. E. Wolf; *CHU Purpan, Toulouse* (3): P. Bernader; *CHU, Bordeaux* (2): P. Besse; *Clinique Volney, Rennes* (2): P. Descaves; *CHU Tenon, Paris* (1): A. Vahanian.

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*Numbers in parentheses are number of study patients; all participating centers are in France.

The Journal of
Invasive Cardiology

www.invasivecardiology.com

Volume 14/Number 6 June 2002

The Official Journal of the International Andreas Gruentzig Society

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ISSN 1042-3931

The Journal of Invasive Cardiology is a peer-reviewed journal publishing advances in invasive cardiology. All articles submitted are blindly peer-reviewed by our editorial advisory board.

Editorial Correspondence — Article submissions should be forwarded to Laurie Gustafson, Executive Editor, the Journal of Invasive Cardiology, Editorial Office, 3298 Winterberry Rd., West Bloomfield, MI 48324. Tel. 248-360-2777, FAX 248-360-2266, E-Mail: Laurie3JIC@aol.com

The Journal of Invasive Cardiology (ISSN 1042-3931) is published monthly by HMP Communications, 83 General Warren Blvd., Suite 100, Malvern, PA 19355. Printed in USA at Dartmouth Printing, 69 Lyme Road, Hanover, NH 03755.

POSTMASTER: Send address changes to the Journal of Invasive Cardiology, 83 General Warren Blvd., Suite 100, Malvern, PA 19355.

The Journal of
Invasive Cardiology

JUNE 2002 • Volume 14/Number 6

Original Contribution

Rotablator® Versus Cutting Balloon® for the Treatment of Long In-Stent Restenoses

Peter Braun, MD, Erika Stroh, MD, Karl-Wilhelm Heinrich, MD

ABSTRACT: **Conventional balloon angioplasty of in-stent-restenoses (ISR) will result in 50–70% re-restenoses. In addition to intracoronary brachytherapy, several ablative and non-ablative interventional technologies have been proposed to manage diffuse ISR. This study was designed to retrospectively assess rotational coronary atherectomy (Rotablator®, or RA) and the Cutting Balloon® (CB) with respect to the rate of restenoses after 6 months, the need for any additional revascularization at the target lesion (TLR), and the frequency of major cardiac events.** ***Methods.*** **To compare both techniques, we used the RA to treat 51 consecutive patients with long (> 10 mm) ISR. Subsequently, 76 patients with identical indications were treated with the CB. Both groups were comparable with respect to their coronary morphologies, demographic and clinical data.** ***Results.*** **Re-angiography was performed in 86% of patients in the RA group and in 72% of patients in the CB group. On quantitative coronary angiography (QCA), the rate of restenoses was 63.9% in the RA and 27.3% in the CB group; the difference was statistically significant ($p < 0.01$). The rate of re-TLR was also significantly lower (18.7%) in the CB than in the RA group (43.2%). The rate of major cardiac events (not requiring TLR) was not different between both groups (CB = 7.3%; RA = 9.1%).** ***Conclusion.*** **Even when the methodological constraints of retrospective studies are taken into account, the study data indicate that treating diffuse ISR with the CB results in an acceptable long-term outcome and a low complication rate, results which make this method appear superior to RA.**

J INVAS CARDIOL 2002;14:291–296

Key words: cutting balloon, restenosis, rotablator

In comparison to conventional balloon dilatation, intracoronary stents reduce the rate of restenoses and periinterventional complications for specific vessel segments and in vessels with a diameter of > 3 mm. The lower rate of restenoses after stent placement is due to a larger diameter gain and smaller recoil than with just balloon dilatation. Both factors result in a larger net lumen, despite increased intimal proliferation. Depending on the characteristics of the original lesion, one can expect in-stent restenosis (ISR) in 10–40% of cases after stent implantation. One-third of such ISR are focal, and two-thirds are diffuse, extending throughout the stent. While the treatment of focal ISR with conventional balloon angioplasty has acceptable results, the management of diffuse ISR by PTCA is characterized by restenosis rates of up to 70%, making such lesions an unsolved problem for the interventional cardiologist.[1] The final clinical value of intracoronary brachytherapy — especially with respect to its long-term outcome — remains undetermined, despite encouraging initial results.

Numerous attempts have been made to treat diffuse ISR with other interventional modalities. Based on theoretical considerations, primarily ablative technologies such as atherectomy, laser angioplasty and Rotablator® (RA) (Boston Scientific, Redmont, Washington) appeared suitable to re-open the lumen sufficiently despite the thickened neo-intimal layer. For example, RA was shown to have a low complication rate when used to treat ISR.[2] When the Cutting Balloon® (CB) (Boston Scientific), a non-ablative technique, was evaluated for the management of diffuse ISR, the primary results were good and the complication rate was low.[3,4] Several studies have compared both RA and CB with conventional balloon angioplasty, however, studies comparing alternative treatments for ISR are scarce.[5,6]

In order to compare the short- and long-term results of these treatment modalities, we performed a longitudinal study. Initially, a number of consecutive patients presenting with symptomatic, diffuse ISR were managed with the RA. During the second phase, all patients with identical presentation were treated with the CB. In both groups, the restenosis rate was determined angiographically, the frequency of major coronary events (MACE) was assessed, and the rate of required reinterventions (at the TL) was determined.

From the Department of Cardiology and Angiology, Duisburg Heart Center, Duisburg, Germany.

Manuscript received September 21, 2001, provisional acceptance given January 16, 2002, revised manuscript accepted May 11, 2002.

Address reprint requests to: Peter Braun, MD, Department of Cardiology and Angiology, Duisburg Heart Center, Gerrickstr. 21, 47137 Duisburg, Germany. E-mail: peter.braun@ejk.de

MATERIALS AND METHODS

Patient population. A total of 127 patients (Table 1) presenting with symptomatic, long (> 10 mm) ISR were treated (89 males, 38 females). From August 1996 to May 1998, a total of 51 consecutive patients were treated with the RA; from June 1998 to June 2000, there were 76 consecutive patients managed using the CB. During each treatment period, all patients with symptomatic long ISR (as determined by online QCA) were treated with the corresponding treatment technique without any further selection except of the time point of treatment. There were no crossovers between treatment groups.

Both patient groups were not different with respect to age, gender, vessel affected, and the ratio of diabetics and history of myocardial infarction (Table 1). Regarding the characteristics of the coronary lesions, such as length, minimal luminal diameter (MLD), stent length, stent size, etc. (Table 2), the treatment groups were also not significantly different. Just the spectrum of stents found to be restenosed was somewhat different, because of the different time periods. Multilink® stents (Guidant Corp., Indianapolis, Indiana) and GFX® stents (Medtronic Inc., Minneapolis, Minnesota) were the most frequently found stents in both groups.

Treatment methods

RA. Rotational angioplasty was performed using the Rotablator® system. Before the intervention, all patients received 10.000 IU of heparin iv and several boluses of ic nitroglycerin, as tolerated by blood pressure, into the target vessel. For interventions on the RCA, a transvenous pacemaker lead was positioned in the apex of the right ventricle. All patients were on an oral medication of 100 mg of aspirin od, which was continued after the procedure.

An average of 1.22 rotablator burrs were used per case; the average size was 2.14 mm. Depending on the maximum burr size, 8 French (Fr) or 9 Fr guiding catheters were selected. Following rotablation, balloon dilatation completed all procedures. The average balloon size was 3.09 mm and the mean inflation pressure 4.8 ATM (71 psi). The burr-to-stent ratio was 0.73, the burr-to artery ratio was 0.84 and the balloon-to-artery ratio was 1.23. In all cases, the rotation rate was between 150,000–170,000/minute. The initial success rate was 100% (51 of 51). No major acute complications were seen.

CB. The Cutting Balloon® was used. At the beginning of the procedure all patients received a bolus of 10.000 IU of heparin iv and a bolus of nitroglycerin into the target vessel. All patients were on an oral medication of 100 mg of aspirin od, which was continued after the procedure. In order to position the CB inside the stent, four cases required pre-dilatation with a small balloon. Only one CB was needed in each case. CB size was based on stent size (CB-to-stent ratio = 1.01). The average CB was 3.05 mm in size (CB-to-artery ratio = 1.18). Mean inflation pressure was 6.12 ATM (90 psi). In 42 cases (55%), a 10 mm CB was utilized, a 15 mm CB in 34 cases (45%). Aiming to improve the angiographic result, the vessel was further dilated with a conventional balloon of identical size (mean inflation pressure = 6.4 ATM; 94 psi) in 11 cases. The primary rate of success was 100% in this group as well, and no significant acute complication occurred.

In accordance with institutional guidelines, informed consents were obtained from all patients.

Quantitative coronary angiography. Treated vascular segments were analyzed with quantitative coronary angiography, using the QUANTCOR system (Siemens, Erlangen, Germany), which is based on the sufficiently validated CAAS II system. Data analysis was performed offline, after completion of the follow-up studies, and the observer was blinded. Angiographic data had been obtained after vasodilatation with intracoronary nitroglycerine, imaging the segments with the least possible axial distortion and overlap. For calibration, the native guiding catheters (no contrast agent) were used as a reference. Identical projections to the ones utilized for the initial intervention were used during follow-up. The following parameters were assessed: reference segment diameter, length of lesion, MLD and percent stenosis. Lesion length was measured from "shoulder to shoulder".

Statistical analyses. All parameters lumped in each group are expressed as mean values ± standard deviation, or — when appropriate — as median values. For comparative statistics of categorical data (restenosis), Fisher's exact test was used. Data with p-values of < 0.05 were considered statistically significant. For comparison of continuous variables, the t-test for independent variables was utilized. Main statistical endpoints were the rate of restenosis and TLR. Major cardiac complications (acutely occurring during the intervention, subacute thromboses, myocardial infarctions, and death, without TLR) represented secondary endpoints.

RESULTS

Acute interventional results. In all cases, the treatment was primarily successful (i.e., resulting in less than a 50% residual stenosis and not causing any acute complications). The analysis of the study parameters before and after the interventions are summarized in Tables 2 and 3. It is evident that none of the pre-interventional QCA measurements differ significantly between the groups. The initial conditions with respect to the degree of stenosis, MLD and reference size were identical; only the lesions were slightly longer in the RA group (11.10 mm vs. 14.07 mm). Five percent of patients in the RA group and four percent in the CB group had chronic total occlusions.

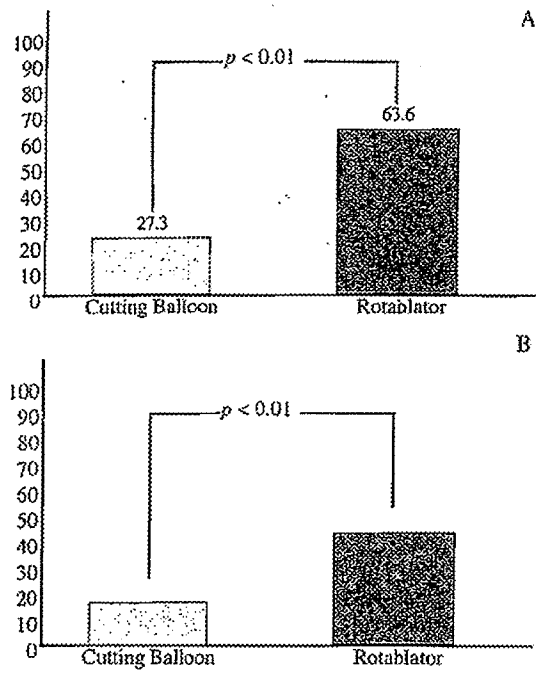

Figure 1. *(A) Restenosis rates. (B) Target lesion revascularization rates.*

By QCA, post-intervention MLD is remarkably larger in the CB group (2.23 mm vs. 2.04 mm; $p = 0.03$). As the pre-interventional MLD and reference values were identical, this translates into significant differences with respect to luminal gain (MLD, post-MLD, pre), which was 1.58 mm in the CB group vs. 1.42 mm in the RA group ($p = 0.03$).

Follow-up angiography after 6 months. Re-angiography was planned for all cases; it was performed in 55 of the 76 patients in the CB group, and in 44 of the 51 patients in the RA group. The angiographic follow-up rate was 72.4% and 86.3%, respectively. The median follow-up interval was 181 (CB) and 180 days (RA).

At the 6-month follow-up examination, QCA results showed a significantly larger MLD (1.59 mm; $p = 0.03$) in the CB groups than in the RA group (1.15 mm). At the 6-month follow-up examination, QCA results showed a significantly larger MLD (1.59 mm; $p = 0.03$) in the CB group than in the RA group (1.15 mm) leading to a highly significant group difference for percent diameter stenosis ($p < 0.01$; Table 4B). In the CB group, neither loss in stenosis reduction nor MLD increase/loss index were significantly superior to the RA group. The rate of angiographic restenosis calculated from the follow-up studies was 27.3% in the CB group, which is significantly ($p = 0.01$) lower than the 63.6% restenosis rate observed in the RA group (Figure 1A).

Table 1. Baseline demographic data of all patients

Cutting Balloon	Rotablator	
Number of patients	76	51
Male 51 (67%)	38 (75%)	
Female 25 (33%)	13 (25%)	
Age 62.8 ± 7.5*	64.7 ± 8.8*	
History of myocardial infarction	18 (24%)	13 (26%)
Diabetes mellitus	12 (16%)	7 (14%)

* = standard deviation

Table 2. Lesion and stent characteristics before intervention

	Cutting Balloon*	Rotablator*
Mean stent diameter	3.05 ± 0.26*	3.03 ± 0.31*
Mean stent length	15.6 ± 3.68*	15.4 ± 4.22*
Stent type		
Gfx	38.2%	60.6%
Multilink	29.1%	21.4%
Tenax	9.2%	0%
Crossflex	7.9%	2%
Paragon	2%	0%
PS	1.2%	2%
Inflo	2.6%	4%
Bard XT	4%	4%
Synthesis	4%	4%
Be-Stent	1.8%	2%
Stented vessel		
LAD	40%	55%
LCX	25%	12%
RCA	29%	29%
RD	4%	4%
SVG	2%	0%
Lesion characteristics		
Reference diameter (mm)	2.72 ± 0.55*	2.66 ± 0.50*
Lesion length (mm)	14.7 ± 5.1*	17.2 ± 6.7*
MLD (mm)	0.65 ± 0.32*	0.62 ± 0.34*
% diameter stenosis (%)	76.1 ± 11.4*	77.8 ± 11.5*
Chronic occlusions	5%	4%

* = standard deviation

Six-month follow-up clinical endpoints. Indications for repeat interventions were based on both angiographic follow-up and on the clinical status. On follow-up, 44% of the CB vs. 56% of the RA patients experienced symptoms suggestive for myocardial ischemia, which was confirmed in 17% and 35%, respectively, by exercise electrocardiography, stress echocardiography, or radionuclide scans. Subsequently, percutaneous interventions or surgical bypass procedures were required in 18.7% of patients in the CB group and in 43.2% of patients in the RA group ($p < 0.01$ (Figure 1B).

Complications and major events. Immediately after the intervention (within 24 hours), no major events were observed in either group. Puncture site hematomas not requiring any intervention and mild CK elevations — up

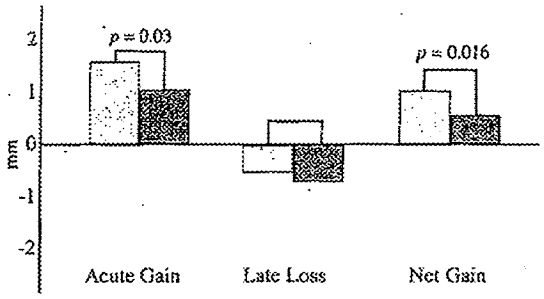

Figure 2. *Changes of acute gain, late loss and net gain in both treatment groups (ns = not significant)*

to 2.5 times the normal value — occurred in both groups with the expected frequencies.

While in the hospital on the second day after the intervention, one CB group patient developed signs of an acute myocardial infarction due to an acute occlusion of the target lesion. Immediate PTCA resolved the problem without adverse consequences; CK levels remained less than 2.5 times normal. Two patients expired within the 6-month follow-up period between the intervention and the scheduled angiographic check-up (one in each group). The cause of the CB patient's death remains unclear; the death in the RA group was most likely cardiac.

Within the follow-up period, two patients in the CB group and 3 in the RA group experienced acute myocardial infarctions. In one case in each group, the target lesion under observation for this study was responsible. The rate of major cardiac events (excluding TLR) was 7.3% in the CB group and 9.1% in the RA group; therefore, within the expected range for this population.

DISCUSSION

Achieving good long-term results when treating long ISR is the most important unresolved question in the field of interventional cardiology. Long ISR represent a new disease entity. Because of the unacceptable restenosis rate, conventional balloon angioplasty is not the proper treatment modality for this particular disease process.[4,7,8]

The real value of intracoronary brachytherapy remains controversial, although encouraging initial results have been accomplished with β- or γ-rays. The long-term outcome is undetermined, though, and the method is logistically challenging.

Three processes are known to contribute to restenoses: vascular remodeling, elastic recoil, and intimal proliferation. For ISR formation, only intimal proliferation is of any quantitative significance.

From a pathophysiological point of view, the use of ablative technologies, such as directional coronary atherectomy, laser angioplasty, or RA, would appear favorable for treating ISR. So far, only RA has been evaluated in a study with sufficient patient enrollment (ARTIST trial), not counting case reports.

In addition to other (non-ablative) techniques, CB has also been proposed and evaluated by some authors as a possible treatment option for patients with long ISR. It was shown that either RA or CB could be used in ISR with successful outcomes and low complication rates.[4,9-13] However, long-term data and figures on the frequency of restenosis are lacking, especially data comparing both methods. Only Briguori et al.[5] and Adamian[6] compared matched groups and showed that CB resulted in lower restenosis rates than conventional balloon angioplasty and RA. Colombo's study did not asses the differences between short and long ISR. Our study was designed to retrospectively compare the frequency of restenoses, MACE, and TLR at 6 months, between groups treated with either technique.

Although the study design was retrospective and not randomized, the study groups were shown to be comparable with respect to their demographic and angiographic characteristics (Table 1). For each treatment period, the only selection criterion was the time point of the intervention, which excluded any other selection bias for either treatment option. The type, length, and size of the restenosed stents were

Table 3A. Cutting Balloon, interventional parameters

Cutting Balloon	
Mean balloon diameter (mm)	3.05 ± 0.29*
Ballon /Artery Ratio	1.18 ± 0.21*
Ballon/Stent Ratio	1.01 ± 0.06*
CB length = 10 mm	55%
CB length = 15 mm	45%
Predilatation	5%
Max. dilatation pressure (bar)	6.24 ± 0.94*
Mean duration of dilatation (seconds)	112 ± 14*

* = standard deviation

Table 3B. Interventional parameters for Rotablator, treatment

Rotablator	
Number of burrs	1.22 ± 0.42*
Max. burr size (mm)	2.14 ± 0.84*
Max. Burr/Artery Ratio	0.84 ± 0.79*
Max. Burr/Stent Ratio	0.73 ± 0.66*
Rate of postdilatation	100%
Balloon size for postdilatation (mm)	3.09 ± 0.37*
Balloon/Artery Ratio	1.23 ± 0.61*
Balloon/Stent Ratio	1.03 ± 0.09*
Max. inflation press. (bar)	7.24 ± 1.24*
Duration of inflation (seconds)	94 ± 21*

* = standard deviation

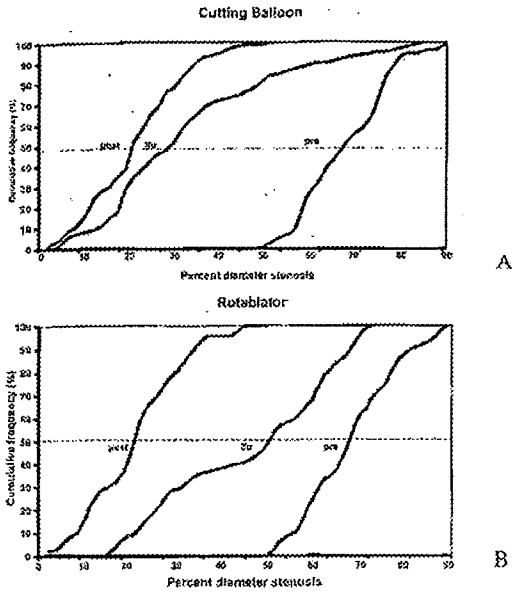

Figure 3. (A) Cutting Balloon®, percent stenosis, cumulative frequency. (B) Rotablator®, percent stenosis, cumulative frequency. Pre = prior to intervention; post = directly after intervention; fu = at follow-up

Table 4A. QCA-analysis of interventional results

Interventional Results	Cutting Balloon	Rotablator	p
Reference diameter (mm)	2.76 ± 0.46*	2.77 ± 0.4*	0.77
Lesion length (mm)	11.1 ± 5.01*	14.07 ± 7.74*	0.14
MLD (mm)	2.23 ± 0.48*	2.04 ± 0.46*	0.03**
% diameter stenosis	20.16 ± 11.64*	23.33 ± 11.17*	0.12
Acute gain (mm)	1.63 ± 0.43*	1.42 ± 0.54*	0.03**
Stenosis reduction (%)	57.46 ± 13.53*	54.09 ± 19.05*	0.31

* = standard deviation, ** = $p < 0.05$

Table 4B. QCA-analysis of follow-up results

Follow-Up Results	Cutting Balloon	Rotablator	p
Mean time to fu (days)	159 ± 22*	191 ± 25*	0.45
Median time to fu (days)	181	180	0.72
Reference diameter (mm)	2.68 ± 2.31*	2.54 ± 0.99*	0.24
Lesion length (mm)	10.57 ± 6.83*	14.28 ± 7.3*	0.64
MLD (mm)	1.59 ± 0.98*	1.15 ± 0.73*	0.03**
% diameter stenosis	28.8 ± 19.11*	47.2 ± 21.9*	0.003***
Loss in stenosis reduction	20.35 ± 26.71*	31.11 ± 29.74*	0.06
Late loss (mm)	0.64 ± 0.35*	0.89 ± 0.37*	0.19
Net gain (mm)	0.94 ± 0.52*	0.53 ± 0.29*	0.016***

* = standard deviation, ** = $p < 0.05$; *** = $p < 0.01$

Table 5. Symptoms and serious events during time to follow-up

	Cutting Balloon	Rotablator	p
Clinically symptomatic at fu	44%	56%	ns
Ischemia in area of target vessel	17%	35%	ns
All serious events	7.3%	9.1%	ns
Subacute thrombosis	1.8%	0	ns
Death	1.8%	2.3%	ns
Myocardial infarction	3.7%	6.8%	ns

ns = not significant; fu = follow-up

also not significantly different throughout the study period (Table 2).

However, when analyzing the QCA data obtained right after the intervention, it is evident that CB treatment has significantly better immediate results with respect to MLD and acute luminal gain (Table 4A). This may be surprising at first, as CB represents a non-ablative technique. CB appeared to extrude the plaque material better through the stent struts after the segmentation of the plaque by its blades than did conventional PTCA following ablation using RA, even if the average inflation pressure was somewhat lower in the CB group (Tables 3A and 3B).

The follow-up rates of 70% and 85% were acceptable in both groups. At the scheduled follow-up, there was a trend for patients belonging to the RA group to be more symptomatic and have more frequent objective markers for ischemia related to the vessel originally targeted.

In comparing QCA studies obtained at the 6-month follow-up, it was shown that the original MLD difference, which favored CB, did not only persist, but in fact increased. Figure 2 depicts graphically how a significantly larger net luminal gain results from a significant initial luminal gain augmented by a relatively smaller late luminal loss. As elastic recoil is certainly not a significant contributor for restenosis when treating ISR, one can only conclude that the lower loss of MLD (late loss) after CB is secondary to less intimal proliferation. This conforms to the hypothesis that CB treatment results in less neointimal proliferation because of less intimal trauma.[14] In the CB group, reference segment data are unchanged upon follow-up, the average length of the stenoses is somewhat smaller, but the changes in percent stenoses and MLD's differ significantly (Table 4A).

Plots of the frequency distribution of percent stenoses and MLD (Figures 3 and 4) clarify the better initial gain and late loss in the CB group. This translates into a significantly lower restenosis rate of 27.3% in patients treated with the CB vs. 63.6% (Figure 1A). At first sight, a restenosis rate of over 60% in the RA group seems to be surprisingly high, but it confirms the result of the ARTIST trial, which represents the largest controlled trial of the RA in the treatment of in-stent restenosis.[15] In this study, RA therapy showed a restenosis rate of 65%.

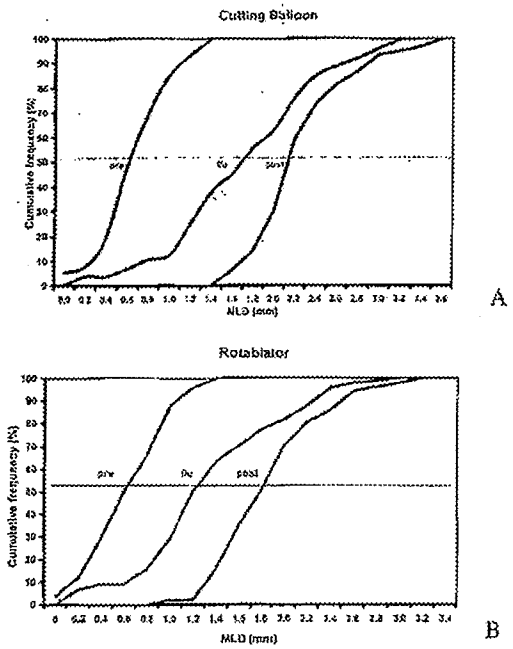

Figure 4. *(A) Cutting Balloon®, MLD, cumulative frequency. (B) Rotablator®, MLD, cumulative frequency. MLD = minimal luminal diameter; pre = prior to intervention; post = directly after intervention; fu = follow-up*

Because clinical symptoms as well as objective ischemia were less frequent in the CB group, the groups are also significantly different with respect to any need to revascularize the targeted segment (18.7% vs. 43.2%) (Figure 1B). In CB patients, TLR occurred with the same order of magnitude as in coronary brachytherapy. During the study period, the rate of major adverse events (MACE without TLR) was identical in both groups (CB = 7.3%; RA = 9.1%) and conformed to our expectations (Table 5).

Even when the methodological disadvantages inherent in non-randomized studies are considered, the clear-cut differences between the groups seem to indicate that CB treatment of long ISR is associated with a better long-term prognosis than RA. The comparable good results for brachytherapy and CB with respect to ISR suggest that both techniques need to be compared in a controlled study. As CB treatment is associated with much lower logistic, technical, and financial expenditure, it may very well turn out to be a valid alternate technique for some subgroups which still need to be identified.

On the other hand, if the above proposed hypothesis holds true that CB treatment leads to less intimal proliferation as compared to conventional balloon angioplasty, pretreatment of diffuse in-stent restenosis before brachytherapy may be a preferable treatment option.

CONCLUSION

Because of poor long-term results, conventional balloon dilatation is not suitable for treating long ISR. In this retrospective comparative study, CB resulted in a significantly better outcome after 6 months with respect to rate of restenosis and TLR. The low restenosis rates and lower need for TLR suggest that a comparative study on CB vs. coronary brachytherapy would make sense, especially because of the much lower expenditure needed for treating long ISR with CB.

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Inter Partes Reexamination No. 95/001,095
Declaration of Antonios G. Mikos, Ph.D.
Exhibit 2

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Cardiovascular Research 35 (1997) 405–413

Cardiovascular Research

Review

Local drug delivery systems and prevention of restenosis

David Brieger, Eric Topol *

Department of Cardiology and the Joseph J. Jacobs Center for Vascular Biology, The Cleveland Clinic Foundation, 9500 Euclid Ave, Desk F-25, Cleveland, OH 44195, USA

Received 11 February 1997; accepted 3 June 1997

Keywords: Restenosis; Percutaneous coronary revascularization

1. Introduction

It is somewhat incongruous that the successful performance of percutaneous transluminal coronary revascularization, a technically challenging and somewhat delicate endeavour, is predicated on the delivery of a traumatic insult to the vascular wall. This injury incites a cascade of compensatory responses, involving thrombosis and inflammation, vascular smooth muscle proliferation and migration, and matrix production and deposition. Although this reparative process usually stabilizes the site of injury and ensures a successful long term result, in 30 to 50% of cases it is excessive [1], resulting in compromise of the lumen with the potential for recurrent ischemia.

Our understanding of the process of restenosis, although not yet complete, has evolved considerably in recent years. There is a complex interplay of vessel wall remodeling and neointimal proliferation. Remodeling refers to a contracture or 'shrinkage' of the vessel, primarily related to the inflammatory process in the vessel wall which involves the media and adventitia. The neointimal proliferative process appears to be linked to vascular smooth muscle cell activation, proliferation and migration [2,3]. The deployment of an intracoronary stent at the site of injury, by providing a scaffold within the vessel wall, can reduce the impact of vascular remodeling, but may be accompanied by an exhuberant intimal hyperplastic response [4] with consequent restenosis in a persistent 20–30% of cases [5,6].

Thus, over recent years there has been a widespread intensive research effort directed towards identifying pharmacotherepeutic regimens targeting primarily (but not exclusively) the smooth muscle cell, to prevent the neointimal restenotic process. These have involved conventional pharmacological agents, as well as novel gene therapies, and many of these have been found to be effective in preventing restenosis in animal models of vascular injury following systemic administration. However, when these agents have progressed to clinical trials, the results have been almost universally disappointing [1].

The concept of local drug delivery was spawned by the observation that many of the therapies successfully tested in animal models were only effective at doses far greater than could safely be applied to patients. It was postulated that by confining the therapeutic agent to the site of injury, greater local concentrations could be achieved with reduced potential for systemic toxicity. Several elegant animal studies provided validation of this hypothesis, however, the successful translation of this to a viable clinical strategy has been technically challenging. Major obstacles that have been encountered include: (1) the design of devices that enable delivery of adequate quantities of drug to the vessel wall without either injuring the wall or compromising flow, (2) the development of delivery vehicles that allow retention of the administered drug within the local environment for periods of time adequate to ensure a therapeutic effect, (3) the optimization of strategies enabling the transfer of genetic material into cells within the vessel wall, and (4) the development of sustained delivery polymeric coatings for stents that do not produce thrombosis or an inflammatory tissue response.

2. Validation of the concept of local drug delivery

Some of the most insightful work in the area of pharmacotherapy for the prevention of restenosis has been pro-

* Corresponding author. Tel.: +1 216 4459490; Fax: +1 216 4459595; E-mail: topole@ccsmtp.ccf.org

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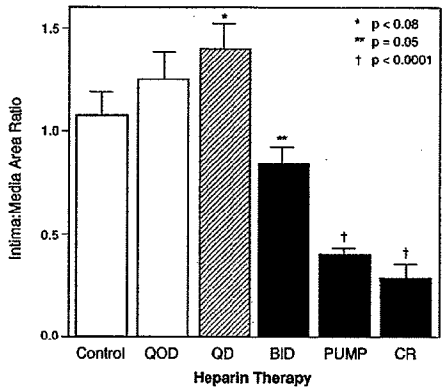

Fig. 1. In a rat model of vascular injury, intimal hyperplasia is exacerbated by intermittent injections of heparin and relieved by continuous administration of a higher dose or local administration from controlled release polymer matrices. QOD: every other day, QD: every day, BID: twice daily, PUMP: continuous administration via osmotic pumps, CR: continuous release into the perivascular space from controlled release polymer matrices. Adapted from [9], with permission.

vided by Edelman et al., focusing on the antithrombotic and antiproliferative agent heparin. Clinical trials of this agent had surprisingly shown it to have little impact, or even increase the incidence of restenosis relative to placebo in patients undergoing coronary angioplasty [7,8]. In a rat model of vascular injury, Edelman et al. showed that heparin administered subcutaneously at doses (1 mg/kg) and time intervals comparable to those used in clinical trials, exacerbated rather than alleviated intimal hyperplasia. However, both a continuous infusion of a larger dose (7.2 mg/kg/day), or perivascular administration of heparin via a surgically implanted polymeric device, significantly reduced the degree of both intimal hyperplasia and intimal cell proliferation (Fig. 1), supporting the contention that pharmacokinetic considerations, in part, may explain the disparity between animal model data and clinical trial experience [9]. In addition, in contrast to intermittent subcutaneous administration, neither continuous intravenous infusion nor the local delivery of heparin prolonged the activated partial thromboplastin time, indicating that it was possible for a local beneficial effect to be uncoupled from unwanted systemic side effects. Further evidence supporting the ability of locally delivered agents to impact upon restenosis was provided by Villa et al. who periadventitially wrapped dexamethasone impregnated silicone polymers around the carotid arteries of rats undergoing balloon injury [10]. Neointimal proliferation was significantly reduced in animals implanted with the glucorticoid-releasing polymer relative to those receiving placebo. Among those receiving active treatment, there was a 2-fold reduction in neointimal hyperplasia at sites covered by silicone matrices compared to the non-covered arterial segments. Therefore, although the effect of the drug was not exclusively site specific, the local delivery of dexamethasone had an incremental impact on neointimal proliferation relative to systemically absorbed drug (Table 1).

Periadventitial delivery systems are ideally suited for small animal research, and may allow the identification of agents that inhibit neointimal proliferation at sites of local delivery after vascular injury [11]. In addition, they may be of value in certain clinical situations such as restenosis occurring within the venous limb of A–V shunts in hemodialysis patients. Because the stimulus for venous neointimal hyperplasia is prolonged (i.e., pressure transmitted from the arterial circulation), sustained release of a drug is desirable and an appropriate drug-containing film can be directly applied to the extravascular surface when the shunt is installed. However, such systems are clearly less appropriate for preventing coronary restenosis. Accordingly, a number of devices have been devised that permit percutaneous, transcoronary application of local therapy at the time of coronary intervention.

3. Local delivery devices (Table 2)

3.1. Balloon catheter delivery systems

3.1.1. Double balloon (Fig. 2a)

The earliest approach to percutaneous local drug delivery involved the use of a double balloon catheter [12]. This device is passed over a guidewire like a conventional angioplasty balloon, the dual balloons are inflated proximal and distal to the site of injury, and drug is infused into the isolated vessel segment between the two balloons. Infusion pressures of 300 mmHg are sufficient for the uptake of agent into the arterial wall without causing local trauma [13] and the device has been used to deliver both pharmacologic agents and genetic material in a variety of

Table 1
Intima/media ratios of arterial segments from 3 groups of rats that underwent balloon injury

	Silicone polymer with 5% dexamethasone		Placebo
	Covered arterial segments	Non-covered arterial segment	
Intima/media ratio (mean ± SEM)	0.26 ± 0.04	0.53 ± 0.08	1.09 ± 0.16

Dexamethasone or placebo impregnated silicone polymers were wrapped around the arteries at the time of injury. For further details see text. Adapted from [10], with permission.

animal models [12,14]. However it suffers from a number of significant limitations: adequate drug delivery in vivo requires inflation times of 15 to 30 min resulting in substantial distal ischemia; the length of the enclosed chamber results in the loss of some drug into side branches when used in the coronary vasculature, and the balloon inflation pressures necessary to seal the compartment may cause additional vessel injury proximal and distal to the target site.

3.1.2. Porous and microporous balloons (Fig. 2b,c).

The standard porous balloon was developed to overcome some of the deficiencies associated with the double-balloon catheter described above [15]. Inflation of a non-

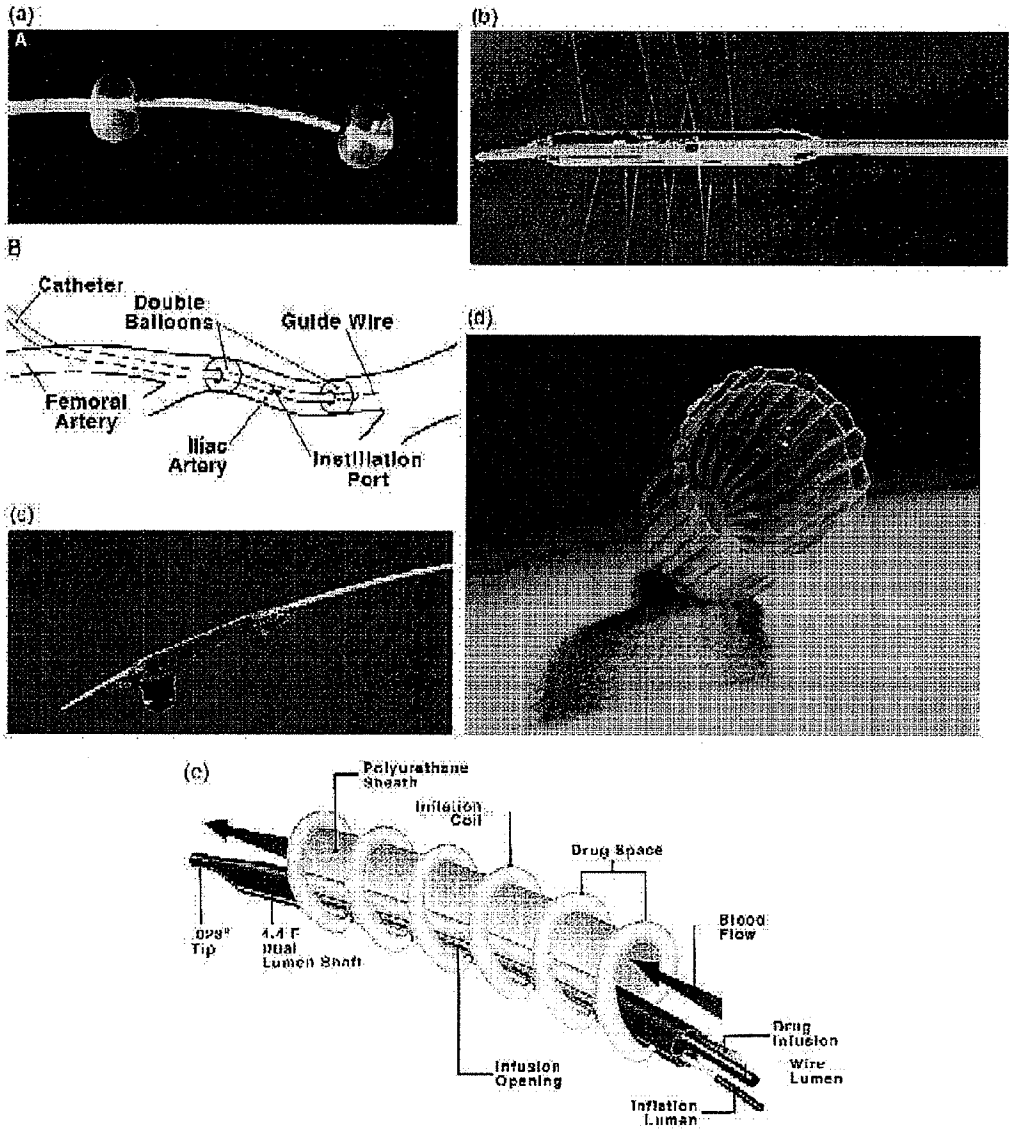

Fig. 2. (A) Photograph of Wolinsky double balloon. Reprinted with permission (Nabel EG, Plautz G, Boyce FM, Stanley JC, Nabel GJ. Science 1989;244:1342–1344). (B) Photograph of porous balloon catheter showing jet streaming during balloon inflation. Reprinted with permission [15]. (C) Photograph of microporous balloon with drug 'weeping' from the balloon at 5 atm pressure. Reprinted with permission (Lincoff AM, Topol EJ, Ellis SG. Circulation 1994;90:2070–2084). (D) Photograph of cross section of a 'channel catheter' with central high pressure inflation chamber and circumferential drug infusion channels [19]. (E) Illustration of Dispatch catheter showing the coil shaped drug infusion balloon with a central perfusion channel. Reprinted with permission (Lincoff AM, Topol EJ, Ellis SG. Circulation 1994;90:2070–2084).

Table 2
Local delivery devices

Balloon catheter systems
Double balloon
Porous and microporous balloons
Channel, transport and sheath balloons
Hydrogel balloon
Dispatch catheter
Mechanical delivery
Iontophoretic balloon
Stents
Polymer stents
Polymer coated metallic stents
Cell seeded stents

compliant balloon containing pores of 25 μm in diameter results in direct delivery of infusate through the pores into the juxtapositioned arterial wall with the depth of penetration directly related to the perfusion pressure (usually between 2 and 5 mm Hg). The major drawback of this device is the potential for vascular barotrauma caused by the fluid jets [16]. This not only results in potential immediate local complications, but may also increase the likelihood of a long-term neointimal response [17]. In normal porcine coronaries, this injury can be minimized by reducing both the volume and pressure of delivery of infusate, without compromising delivery of solute into the vessel wall [18], but it is not clear whether the same is true in atherosclerotic human vessels.

The microporous balloon is a modification of the above, consisting of an inner balloon with an array of 25 μm holes surrounded by an outer membrane with 0.8 μm pores [16]. Although the inflation pressures are comparable to those with the porous balloon (2 to 5 atm), the infusate weeps from the pores in the external membrane, reducing the potential for tissue injury.

The porous and microporous balloon designs share some important limitations. Because both rely on hydrostatic pressure to both to inflate the balloon and infuse the contents of the catheter, significant systemic administration of the solute may occur during balloon inflation and deflation. In addition, the holes in both can become obstructed, resulting in nonhomogeneous solute delivery.

3.1.3. Channel, transport and sheath balloons (Fig. 2d)

Several delivery catheters have been designed with the aim of dissociating drug infusion pressure from that required for balloon inflation. The channel catheter (Boston Scientific Corp) consists of a central balloon surrounded by a series of channels, each with a single 100 μm hole through which the drug can be infused [19]. The Transport coronary angioplasty catheter (Cardiovascular Dynamics) is similar, with a central balloon surrounded by an outer porous balloon for drug infusion [20]. Both these catheters simplify the procedure of post angioplasty local drug delivery allowing the intervention and subsequent pharmacotherapy to be performed sequentially with the same device. Another novel variation consists of an infusion sheath (Infusion Sleeve, Localmed, Inc.) which can be advanced over any standard angioplasty catheter and advanced to the lesion after balloon dilatation [21].

3.1.4. Hydrogel balloon

The hydrogel coated balloon (Boston Scientific Corp) is designed to enable simultaneous lesion dilatation and local delivery [22]. The hydrophilic acid polymer coating has a thickness of 5 to 20 μm when dry and swells by a factor of 3 when exposed to an aqueous solution that may include drugs or genetic material. A thin layer of therapeutic agent is coated onto the balloon, allowed to dry and then 'pressed' into the vessel wall during balloon inflation. Disadvantages of the Hydrogel catheter include its relatively limited drug carrying capacity, and the fact that the drugs are rapidly washed off the balloon on entry into the blood stream, necessitating the application of an effective but somewhat cumbersome protective sheath over the balloon as it is advanced toward the target vessel.

3.1.5. Dispatch catheter (Fig. 2e)

The dispatch catheter (Scimed Life Systems Inc.) consists of an outer helix-shaped infusion balloon with delivery channels that when inflated allows prolonged contact of infusate with the arterial wall in the inter-helical spaces [23]. Distal coronary perfusion is maintained via a central lumen, allowing periods of infusion in excess of 30 to 60 min without causing coronary ischemia. A theoretical disadvantage of this catheter is that the presence of the inflated helical balloon during drug delivery may prevent homogeneous infiltration of solute into the vessel wall. The dispatch catheter has been approved by the Food and Drug Administration in the United States for intracoronary drug infusion.

3.1.6. Mechanical delivery

The iontophoretic balloon relies on an electic current to increase cell permeability and facilitate transport into the vessel wall. The catheter consists of a porous balloon containing the cathode which is advanced across the lesion, and the anode, placed on the skin, is activated with a small electic charge. One preliminary study has shown iontophoresis to result in significantly greater delivery efficiency than obtained by passive diffusion, with minimal vessel wall trauma [24]. A second mechanical delivery system that is undergoing preliminary investigation consists of a catheter with circumferential injection needles, allowing direct application of therapeutic agent into the adventitia where it may persist for weeks after injury. Despite its invasive nature, this device is reported to cause minimal local trauma and no long term intimal hyperplasia [25].

3.1.7. Choice of balloon catheter delivery system

The optimal local delivery device should be simple to use, result in the greatest deposition of drug in the vessel wall without causing local trauma, distal ischemia or systemic administration. On theoretical grounds, both the microporous balloon and those which differentiate inflation from perfusion pressures most closely meet these criteria, although the prolonged dwell times achievable with the Dispatch catheter may prove particularly desirable. It should be noted that many of the delivery systems are in a continuing state of evolution and as they become optimized, well controlled studies comparing various catheter based drug delivery strategies will become imperative.

3.2. Limitations of balloon catheter delivery systems.

3.2.1. Delivery efficiency

Despite the plethora of devices developed to optimize the process of local drug delivery, delivery efficiency, that is the fraction of agent which leaves the catheter and is deposited in the vessel wall, is generally less than 1% [26,27]. However, this still results in a local concentration several hundred fold greater than that in the systemic circulation. In atherosclerotic vessels which have undergone antecedent angioplasty, deposition is into the dissection planes and into side branches and microvasculature. Direct deposition into the intima and media is rarely observed, potentially a major limitation of local drug delivery, however since smooth muscle cell proliferation occurs in areas of arterial dissection, the deposition of active agent at these sites presumably impacts on the restenotic process.

3.2.2. Retention of infused drug

Agents introduced into the vessel wall by local catheter delivery systems may be rapidly washed out over minutes to hours, particularly if they have no specific intramural binding properties [28]. While the issue of retention may not be important for agents like oligonucleotides that permanently affect cell cycle regulation (see below), agents that do not exhibit cell binding properties may be eliminated before they can exert a biologically relevant effect. A number of controlled release matrices have been developed with the goal of prolonging drug residence times within the vessel wall. Most consist of microparticles composed of biodegradable polymers which can be impregnated with drug and are small enough to be administered percutaneously. Once in the vessel wall, the size of the microparticle (5 to 15 μm) prevents elution, and the agent is gradually released. Polymeric microparticles appear capable of dramatically increasing drug residence times, but they may incite an inflammatory response [29]. This may be prevented by reducing the size of the particle, without significantly compromising the retention properties of the compound [30].

3.2.3. Efficiency of gene transfer

Retention of a product may not be so critical for genetic material which, when taken up by vascular cells, may provide prolonged local expression of their products. In order to be effective, a gene must transfect its host cell, so strategies to optimize gene transfer are important components of efficient local delivery systems. A number of gene transfer vectors have been associated with successful in vivo vascular gene transfer, including plasmid DNA alone, plasmid DNA with liposomes, retroviral vectors and adenoviral vectors (Table 3).

Of these, replication defective adenoviruses have resulted in the greatest transfection efficiency, being capable of transfecting 20 to 30% of susceptible cells [31,32]. This vector has been used to successfully transfect a number of genes into different animal models with a salutatory effect on the restenotic process. For example the GAX (growth arrest homeobox) gene encodes transcription factors that maintain the non-proliferative phenotype of vascular smooth muscle cells. The adenovirus mediated local delivery of this gene to denuded rat carotid arteries was shown to significantly reduce neointimal hyperplasia [33]. Similarly, the introduction of the gene encoding the cell cycle inhibitor, cyclin dependent kinase inhibitor CKI p21 via the same vector, resulted in a significant reduction in neointimal formation in a similar animal model [34]. The enzyme herpes simplex thymidine kinase phosphorylates a nucleoside analogue gancyclovir, which is capable of killing dividing cells. In a number of animal models, adenoviral transfer of the gene encoding this enzyme coupled with gancyclovir administration was associated with inhibition of vascular cell proliferation and reduction of neointimal development [35,36]. The retinoblastoma gene product (Rb) inhibits cell proliferation without cytotoxicity in many mammalian cell types and an adenovirus

Table 3
Genes that have been shown to prevent restenosis when delivered by balloon catheter delivery systems in vivo

Gene	Vector	Reference
GAX homeobox	Adenovirus	[33]
Herpes simplex thymidine kinase	Adenovirus	[35,36]
Cyclin dependent kinase inhibitor CKI p21	Adenovirus	[34]
retinoblastoma gene product (Rb)	Adenovirus	[37]
Nitric oxide synthase	DNA liposome with viral particles	[43]

encoding for an active form of Rb was transferred into injured rat carotid and porcine iliac arteries, resulting in decreased neointimal formation [37]. Adenoviral vectors are however highly infectious for a variety of organs, including liver and brain [38,39], and may therefore result in systemic expression of the transgene. They may also incite inflamatory and immune responses [40]. Efforts have been made to modified adenoviruses to reduce their potential toxicity, and second generation products are being evaluated [41].

Transfection efficiency of plasmid DNA with liposomes may be significantly augmented by incorporating inactivated viral particles [42]. This strategy has been used to deliver cDNA encoding endothelial cell nitric oxide synthase to the vessel wall in balloon injured rat carotids [43]. The transfected vessels expressed comparable levels of NO to uninjured arteries and this was accompanied by a 70% reduction in neointimal formation, reflecting the ability of NO to inhibit smooth muscle cell migration and proliferation. Additional strategies to optimize gene transfer undergoing investigation include the inclusion of tissue specific endogenous promoters, allowing gene expression to be restricted to certain cell types within the arterial segment at the time of transfection.

One somewhat cumbersome approach to gene therapy is to seed the vasculature with cells that have been transfected with the desired gene. Using a double balloon catheter, vascular smooth muscle cells have been implanted into denuded iliofemoral artery segments of pigs in vivo [44], but this has not yet been accomplished in the coronary circulation.

Another promising technique involves the introduction of antisense oligonucleotides into a cell in order to inactivate the mRNA encoding proteins important in the restenotic process. These oligonucleotides comprise short synthetic segments of DNA designed to hybridize with the RNA of interest, preventing its translation. Successful in vivo studies have been reported using antisense oligonucleotides directed against c-mbc and c-myb (nuclear transcription factors), and proliferating cell nuclear antigen and cell cycle specific proteins cdc2 and cdk2 kinases [11,45–47]. Recent studies have suggested the antisense oligonucleotide may exert their activity through non-antisense mechanisms [48], possibly by binding non-target m-RNA and preventing its translation. In addition, the oligonucleotide may be capable of binding intracellular proteins and changing their functional characteristics. The implications of this require further evaluation before this strategy will reach the stage of clinical application.

3.3. Stents

Scaffolding a coronary artery at the site of balloon injury with a stainless steel stent, prevents compensatory vessel wall remodeling and thus eliminates one of the contributing factors toward restenosis. A number of strategies have been developed in order to simultaneously target both neointimal hyperplasia and vessel wall remodeling. Considerable effort has been directed towards developing stents coated with a biodegradable-drug-impregnated polymer, capable of gradually releasing therapeutic agents into the vessel wall. Realizing this goal has been difficult, as a number of polymers, although biocompatible in other settings, excite an extensive inflammatory response when implanted in porcine coronary arteries [49,50]. Recently however, several polymers, such as poly-L-lactic acid, fibrin and a polyamine-dextran sulphate trilayer have shown some promise [51–53]. In the recent Benestent II pilot study, implantation of a polyamine-dextran sulphate coated stent to which heparin was covalently bound in 207 patients was associated with an overall 6 month restenosis rate of 13% [54]. Strictly speaking, this strategy did not involve local drug delivery, as the polymer was non-eluting so the heparin remained attached to the stent, and it is not clear whether the low incidence of lesion recurrence was affected by patient selection, the technique for stent deployment, or the heparin coating [55]. More recently, the reported success of the application of local radiation at the time of PTCA in the prevention of restenosis (see below) has indicated that there is an early window of opportunity to impact upon this process. Therefore, the goals of future drug delivery protocols involving polymeric films applied to stents should incorporate early, short term exposure of moderately high doses as a part of the overall strategy. Sustained release over a long period of time should be avoided if the drug is toxic to the medial or adventitial cells or delays re-endothelialization.

Concerns about biocompatibility of the drug eluting polymers, together with early (what now appears to be largely unfounded) suspicions that long-term implantation of metallic stents could be accompanied by a chronic inflammatory response with adverse local sequelae, prompted development of a coated removable stent. Composed of a nitinol alloy that deploys on cooling and collapses on heating to 55°C, this stent is capable of local drug delivery, but further studies are required to ensure that removal of this device in vivo after drug delivery is not associated with thermal injury [56].

Another theoretical approach to combined stenting-local delivery involves seeding stents with cells engineered to secrete biological products that may impact on the restenotic process. Although genetically engineered endothelial cells have been successfully grown on stents, their purchase appears somewhat precarious, and they are readily sheared off by balloon inflation [57]. So far, in vivo application of this strategy has not been reported.

3.4. Local radiation

Interest in the use of local radiation therapy for the prevention of restenosis was precipitated by the observation a number of benign fibroproliferative disorders that

histologically share characteristics with the neointimal hyperplastic response, respond favorably to low doses of ionizing radiation. Encouraging results have now been reported by a number of investigators using catheter-based systems to deliver low dose endovascular radiation in a range of animal models of vascular injury [58–60]. Sources of both gamma and beta radiation have been used although experience to date has been most extensive with the former. Regardless of the source of radiation, the doses required (< 20 Gy) are less than 25% those used normally for treatment of malignancies.

A number of preliminary clinical studies are underway investigating the use of endocoronary irradiation in patients [61]. The largest of these, the SCRIPPS study, has compared two doses of gamma radiation delivered on an iridium 192 guidewire with control treatment in 55 patients with restenotic lesions following coronary angioplasty. Although the early data from this trial have been encouraging, complete follow-up is awaited.

There are several limitations associated with catheter-based endovascular radiation therapy, including excessive radiation when a gamma source is used, and difficulties ensuring uniform dosimetry at all levels of the vessel wall, particularly when there is an eccentric residual lesion. Radioactive beta-particle emitting stents may overcome some of these disadvantages, while at the same time providing protection against remodeling process. Preliminary encouraging data have been reported in several animal models using radioactive stents to prevent restenosis [62–64], although further studies are required to ensure that the effect on neointimal proliferation is both predictable and sustained before these devices will progress to the stage of clinical trials.

3.5. Future directions

It is perhaps inevitable that our lack of understanding of the complex processes responsible for restenosis, resulted in a 'shotgun' approach to research into its prevention. The plethora of local drug delivery devices, vehicles, and therapies together with the complete absence of standardized data to allow rational comparison between strategies reflects this. As we gradually tease out the mechanisms responsible for the restenotic process, so too should our preventative strategies become more rational. From the point of view of local drug delivery, deciding on optimal therapy may require careful comparison of risk/benefit profiles between different balloon and stent delivery systems, polymer particles of different sizes and characteristics and other novel vectors to enhance delivery efficiency, and between the different vectors for gene therapy. Given the fact that the consistent failure of systemic pharmacotherapy to impact on the restenotic process is, in many instances, likely due to inadequate tissue concentration of biologically active agent, we believe that local vascular delivery will evolve as a vital component of the armamentarium used to prevent restenosis. It will doubtless add to the initial cost of the interventional procedure, but should enhance the ability to achieve a successful long-term result following percutaneous coronary revascularization.

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Guidant Halts Further Development on Actinomycin-D Drug Eluting Stent Program

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Indianapolis, IN - Guidant Corporation (NYSE and PCX: GDT), a global leader in cardi and vascular technology, today reported preliminary results of its international ACTION clinical trial evaluating a drug eluting stent system utilizing actinomycin-D.

Preliminary results of the study indicate that actinomycin-D is not effective in preventing restenosis and patients treated with actinomycin-D eluting stents have an unacceptably high target lesion revascularization rate.

Guidant observed this data during the process of monitoring the clinical follow-up of the first 90 patients enrolled in the study. As a result, Guidant's actinomycin-D drug eluting stent program has been halted. The company will not go forward with an IDE submissic for the U.S. pivotal trial using this compound.

"Guidant's overriding interest is in the well-being of the patients involved in the study," said John M. Capek, Ph.D., president, Vascular Intervention, Guidant Corporation. "We are working closely with the clinicians involved in the study to ensure appropriate follow up for the patients.

"Despite these results for the actinomycin-D program, we continue to see great promise for drug eluting stents, and we believe that the processes, capabilities and strategic direction of Guidant's drug eluting stent program are solid," Capek continued. "We will continue to focus on the more advanced paclitaxel program with Cook Incorporated, which recently completed enrollment of 1,042 patients in DELIVER, and we will pursue the development of other drug eluting stents utilizing Guidant's proprietary elution technology and market-leading stent designs."

Conference Call/Webcast

Guidant will conduct a live webcast today, Thursday, March 7, at 8:30 a.m. EST. The li webcast of Guidant's conference call will be accessible through Guidant's website at www.guidant.com/webcast or at CCBN's individual investor center at www.companyboardroom.com. The webcast will be archived on both websites for futur on-demand replay.

The call will be hosted by Guidant's President and CEO Ronald W. Dollens and will feature a review of Guidant's drug eluting stent program. Also participating on the call w be John M. Capek, Ph.D. and Thomas J. Linnemeier, M.D., Senior Vice President and Chief Medical Officer, Guidant Vascular Intervention.

Guidant Corporation pioneers lifesaving technology, giving an opportunity for better life today to 7 million cardiac and vascular patients worldwide. The company, driven by a strong entrepreneurial culture of 10,000 employees, develops, manufactures and marke a broad array of products and services that enable less invasive care for some of life's most threatening medical conditions.

This release includes forward-looking statements concerning drug-eluting stents and ot progress with them. The forward-looking statements are based on assumptions about many important factors, including new product development, regulatory approvals, litigation and other factors listed on exhibit 99 to the company's most recent 10-Q. As such, they involve risks and uncertainties that could cause actual results to differ materially. The company does not undertake to update its forward-looking statements.

Guidant Press Releases > 2002

Mar 7, 2002

Guidant Halts Further Development on Actinomycin-D Drug Eluting Stent Program

Company to Host Webcast/Conference Call Today

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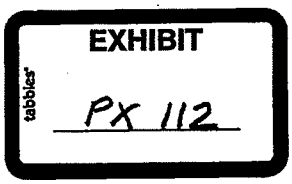

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